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ORIGINAL ARTICLE

Proteus mirabilis urinary tract infection and bacteremia: Risk factors, clinical presentation, and outcomes

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Background/Purpose: *Proteus mirabilis* is a common pathogen responsible for complicated urinary tract infections (UTIs) that sometimes causes bacteremia. Most cases of *P. mirabilis* bacteremia originate from a UTI; however, the risk factors for bacteremia and mortality rates from *P. mirabilis* UTI have not been determined.
Methods: A retrospective, case-control study was performed between May 2008 and November 2010 to identify the risk factors and markers for *P. mirabilis* bacteremic UTI. Each subject in the case group (all patients were diagnosed with *P. mirabilis* bacteremia from a urinary tract source) was matched by age and gender to two subjects in the control group (patients diagnosed with *P. mirabilis* UTI but with negative blood culture results). Clinical presentation and laboratory data were analyzed to determine the risk factors and markers of *P. mirabilis* bacteremic UTI.
Results: Sixty-seven bacteremic UTIs and 124 nonbacteremic UTIs were included in this study. Community-acquired infection ($p = 0.017$), hydronephrosis ($p = 0.017$), band neutrophils accounting for >10% of the white blood cell count ($p = 0.001$), hyperthermia or hypothermia ($p = 0.047$), and a serum C-reactive protein concentration >100 mg/L ($p = 0.002$) were

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identified as independent risk factors for *P. mirabilis* bacteremic UTI. Seventeen patients died in hospital, including 11 in the bacteremic group and 6 in the nonbacteremic group. The bacteremic group had a higher mortality rate ($p = 0.016$). Bacteremic UTI ($p = 0.049$), shock ($p = 0.014$), and a low body mass index (BMI) <18 kg/m^2 ($p = 0.033$) were identified as independent risk factors for mortality.

Conclusion: Because bacteremic *P. mirabilis* UTIs are associated with higher mortality, clinicians should carefully manage cases that present with the risk factors for bacteremia, including community-acquired infection, hydronephrosis, band neutrophils accounting for >10% of the white blood cell count, hyperthermia or hypothermia, and a high level of C-reactive protein.

Introduction

Proteus mirabilis is a member of the *Enterobacteriaceae* family and is a highly motile bacterium.[1] Unlike the other members of *Enterobacteriaceae*, *P. mirabilis* is not a common pathogen that causes urinary tract infections (UTIs) in normal hosts.[2,3] In contrast, *P. mirabilis* is isolated relatively frequently in complicated UTIs, such as those that present in patients with functional or anatomical abnormalities, especially patients with urolithiasis or a chronic indwelling urinary catheter.[4] *P. mirabilis* is well known for its ability to produce urease, which generates ammonia and elevates the pH of the urine to >7.2.[5] Calcium and magnesium crystallization in the urine of alkaline pH blocks the catheter lumen and causes acute urinary retention and the development of bacteriuria and other ascending infections, thereby leading to pyelonephritis, bacteremia, and shock.[6]

P. mirabilis is susceptible to β-lactams, aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole, but is resistant to nitrofurantoin and tetracycline.[7] In recent years, a trend has been observed where *Enterobacteriaceae* species, including *P. mirabilis*, show increased resistance to several antimicrobial agents.[8,9] This increased resistance to antimicrobial agents has led not only to a changes in antimicrobial therapies, but also to poor prognoses and an increase in the mortality rate of hospitalized patients.[10]

Although the risk factors and clinical outcomes of bloodstream infections originating from extended spectrum β-lactamase (ESBL)-positive *Escherichia coli* and *Klebsiella pneumoniae* have been investigated recently,[11–14] bacteremic UTIs caused by *P. mirabilis* are relatively uncommon and, to date, have been less thoroughly studied.[15–17] Furthermore, previous studies show that patients with bactermic UTIs present with more severe systemic inflammatory response syndrome (SIRS) and higher mortality rates than patients without bacteremia.[18,19]

Thus, we conducted a retrospective, matched, case-control study in patients with *P. mirabilis* bacteremic UTIs. The aims of our study were to (1) determinate the relative risk factors of *P. mirabilis* bacteremic UTIs, (2) investigate the risk factors related to mortality, and (3) compare the resistance profiles of *P. mirabilis* between these two groups of patients.

Methods

Study setting and population

Our retrospective, matched, case-control study compares bacteremic and nonbacteremic patients with *P. mirabilis* UTIs who were recruited from the Kaohsiung Medical University Hospital (KMUH), a 1600-bed medical center located in Kaohsiung City in southern Taiwan.

Patients were retrospectively identified from the microbiology databases at KMUH and data were prospectively collected from May 1, 2008 through November 30, 2010. Medical records were reviewed by two infectious disease specialists. Data on the following variables were collected: age, gender, date of admission, diagnosis, outcome, and *in vitro* antimicrobial susceptibility. This study protocol was approved by the Institutional Review Board of KMUH.

Determination of case controls

Patients from whom a urinary culture was obtained, but not a blood culture, and those younger than 18 years of age were excluded. Blood cultures were collected from all enrolled patients. Patients with a positive blood culture from a source other than a UTI, such as a decubitus ulcer or an intra-abdominal infection, were also excluded from this study. Patients with a UTI and bacteremia due to *P. mirabilis* were identified as cases, while patients with a UTI and no bacteremia were identified as controls. Cases and controls were matched for age (±5 years) and sex; the case:control ratio was 1:2.

Case definition

P. mirabilis bacteremic UTIs were defined by a positive urine culture with $>10^5$ colony-forming units (cfu)/mL and isolation of the same strain of *P. mirabilis* from both the urine and blood from the same patient at the same time.[20] Control *P. mirabilis* UTI cases without bacteremia were defined by a positive urine culture in the presence of $>10^5$ cfu/mL accompanied by one of the following: (1) signs of a UTI, such as fever, dysuria, increased frequency of micturition, back or flank pain, or costovertebral angle tenderness; (2) pyuria[21]; or (3) a nonspecific decline in

functions or symptoms that could not be attributed to an obvious source of infection other than UTI.[22]

A patient was considered febrile when the highest recorded tympanic temperature was >38.0 °C on the day the blood culture was collected.[23] Kidney failure was defined as a creatinine level >1.5 mg/dL,[24] and co-morbid conditions (such as cirrhosis, diabetes, etc.) or immunocompromised status were ascertained according to the patient's medical records and Charlson's score;[25] these findings were reviewed by two infectious disease specialists. Nosocomial infections were defined as (1) infections occurring more than 48 hours after hospital or emergency department admission or (2) if patients were referred from another hospital or healthcare facility.[26] Chronic or long-term urinary catheterization was defined as catheterization for more than 7 days prior to specimen collection for bacterial culturing.[27] A urological abnormality was defined as either the presence of urinary tract obstructions, urethral strictures, urolithiasis, benign prostate hyperplasia, congenital abnormalities, or functional problems such as neurogenic bladder or vesicoureteral reflux. A shock episode was defined as a systolic pressure <90 mmHg or the use of inotropic agents to maintain blood pressure for at least 1 hour.

Imaging studies of every case were reviewed whenever possible, and abdominal computed tomography (CT) scan, kidney, ureter, and bladder (KUB) x-rays, or sonographic results were all recorded. We tried to identify whether hydronephrosis or urolithiasis was present in each case. The initial antimicrobial therapy was considered appropriate if at least one antimicrobial agent was active *in vitro* according to Clinical and Laboratory Standards Institute (CLSI) guidelines and was administrated within 48 hours after all samples were collected for culturing.[27] During the study period, a patient was considered to have had two individual episodes when there was complete remisson of fever, leukocytosis, and local signs of infection more than 1 month after the discontinuation of any antimicrobial therapy that was administered to treat the first UTI episde.[28]

Microbiological methods

Blood culture samples were collected in aerobic and anaerobic bottles and were cultured using the BACT/Alert 3D system (Becton Dickinson Microbiology Systems, Sparks, MD, USA). The Vitek 2 System (Biomerieux, Durham, NC, USA) was used to identify and determine the antibiotic susceptibility of the *P. mirabilis* isolates. Susceptibility results were interpreted as sensitive, intermediate, or resistant to antibiotics, according to CLSI criteria.[29]

Multi-drug resistant (MDR) isolates were defined as isolates resistant to or with intermediate susceptibility to more than three classes of the following antimicrobial groups: (1) ampicillin, amoxicillin/clavulanate, or piperacillin/tazobactam; (2) cefuroxime, ceftriaxone, or cefepime; (3) carbapenems; (4) ciprofloxacin or levofloxacin; (5) gentamicin or amikacin; and (6) cotrimoxazole.[30]

Statistical analysis

All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed using the Student *t* test for continuous variables and Fisher's exact test and Pearson's χ^2 test for categorical variables. Significance was set at $p < 0.05$ using two-sided comparisons. All significant ($p < 0.05$) variables that were identified by univariate analysis were further analyzed by multivariable analysis for logistic regression.

Results

During the study period, a total of 740 *P. mirabilis* bacteremic and nonbacteremic UTI cases were evaluated, but only 656 cases remained after the exclusion of isolates from patients under 18 years of age. The causes of the bacteremia in 18 of the 85 cases of *P. mirabilis* bacteremia were thought to be unrelated to the initial UTI. Therefore, 67 episodes were included in the bacteremic group. Among 571 cases of *P. mirabilis*-induced bacteriuria, 447 episodes lacked concurrent blood culture data or were suspected to reflect colonization and were therefore excluded. Cases were matched, as much as possible, for sex and age to 124 controls (bacteriuric episodes with definitively negative blood culture results) in a 1:2 ratio. A total of 191 cases were included in our study, including 67 in the bacteremic group (35.07%) and 124 (64.9%) in the nonbacteremic group. Six patients had two episodes each during the study period (i.e., a total of 191 episodes in 185 patients).

The demographic and clinical characteristics of the patients are shown in Table 1. Of 191 episodes, 60 patients were admitted to intensive care units (ICUs). Among these, 24 were in the bacteremic group and 36 were in the nonbacteremic group. Of these 191 episodes, 147 (77.0%) cases received imaging studies. Nearly half of the cases (49.0%) underwent abdominal sonography, and in 24.6% of cases the patient underwent an abdominal CT scan. In 2.6% of cases, the patient received only a KUB examination.

Univariate analysis revealed that bacteremic *P. mirabilis* UTIs are more common in patients with community-acquired infections than in those with nosocomial-acquired infections (41.9% vs. 22.4%, $p = 0.011$). Hydronephrosis appeared in 43.3% of patients in the bacteremic group, but in only 12.1% of those the nonbacteremic group ($p < 0.001$). Comparing the bacteremic group with the nonbacteremic group, a higher prevalence of urolithiasis was found in the *P. mirabilis* bacteremic group (44.8% vs. 24.2%, $p = 0.006$). Chronic urinary catheterization was less common in patients with community-acquired infections (26.6% vs. 62.7%, $p < 0.001$) (data not shown). There was no obvious difference in the duration of preadmission symptoms between these two groups ($p = 0.903$) (Table 1). Regarding the clinical presentation, the bacteremic group tended to present with hyperthermia (body temperature >38 °C) or hypothermia (body temperature <36 °C) (76.1% vs. 56.3%, $p = 0.011$), higher blood urea nitrogen (BUN) levels (average 40.44 ± 47.57 mg/dL vs. 25.37 ± 26.37 mg/dL, $p = 0.020$), and azotemia (58.2% vs. 41.1%, $p = 0.035$). A band neutrophil count >10% of the white blood cell (WBC) count was more commonly found in the bacteremic group (22.4% vs. 6.5%, $p = 0.003$). There was no statistically significant difference in terms of the presence of a WBC count >12,000 /μL between the bacteremic and nonbacteremic groups (64.2% vs. 50.8%, $p = 0.105$).

Table 1 Demographic and clinical characteristics of patients with bacteremic and nonbacteremic UTIs caused by *P. mirabilis*

Demographic and clinical manifestations	No. (%) of episodes		Odds ratio (95% CI)	*p*-value
	Bacteremic UTI $n = 67$ (%)	Nonbacteremic UTI $n = 124$ (%)		
Age (y, mean ± SD)	68.16 ± 16.85	70.96 ± 16.09	—	0.262
Sex (female)	41 (61.2)	81 (65.3)	0.84 (0.43−1.62)	0.680
Body mass index <18	16 (23.9)	24 (19.4)	1.31 (0.64−2.67)	0.584
Recent hospitalization[a]	38 (56.7)	75 (60.5)	0.86 (0.45−1.64)	0.725
Hospital stay (d, mean ± SD)	19.47 ± 22.33	17.44 ± 17.49	—	0.502
Clinical condition				
Diabetes mellitus (type 2)	17 (25.4)	44 (35.5)	0.62 (0.36−1.20)	0.205
Kidney failure[b]	17 (25.4)	30 (24.1)	1.07 (0.51−2.23)	0.996
Liver cirrhosis	3 (4.5)	4 (3.2)	1.41 (0.24−7.73)	0.698
COPD	9 (13.4)	13 (10.5)	1.32 (0.53−3.20)	0.710
Malignancy	11 (16.4)	24 (19.4)	0.82 (0.37−1.80)	0.761
Cerebral vascular disease	28 (41.8)	61 (49.2)	0.74 (0.41−1.35)	0.408
Bedridden	34 (50.7)	79 (63.7)	0.59 (0.32−1.12)	0.113
Charlson's score ± SD	6.12 ± 3.87	6.87 ± 4.036	—	0.215
Source of infection				
Nosocomial-acquired infection[c]	15 (22.4)	52 (41.9)	0.40 (0.20−0.79)	0.011*
Urinary tract abnormalities[d]	47 (70.1)	70 (56.5)	1.81 (0.96−3.41)	0.089
Hydronephrosis	29 (43.3)	15 (12.1)	5.55 (2.69−11.49)	<0.001*
Urolithiasis	30 (44.8)	30 (24.2)	2.54 (1.35−4.78)	0.006*
Chronic urinary catheterization[e]	23 (34.3)	52 (41.9)	0.72 (0.39−1.34)	0.503
Shock	21 (31.3)	28 (22.6)	1.57 (0.80-3.05)	0.250
ICU admission	24 (35.8)	36 (29.0)	1.36 (0.73−2.57)	0.423
Inotropic agent use	20 (29.9)	23 (18.5)	1.87 (0.94−3.73)	0.109
Preadmission history				
Symptom onset prior to medical care (d, mean ± SD)	2.29 ± 3.66	2.00 ± 2.16	—	0.903

*$p < 0.05$.
Abbreviations: CI, confidence interval; SD, standard deviation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.
[a] Recent hospitalization: recent refers to hospitalization within the past year.
[b] Kidney failure: defined as a creatinine level >1.5 mg/dL.[24]
[c] Nosocomial infection: (1) infections occurring more than 48 hours after hospital admission or after emergency department admission, or (2) those who were referred from another hospital or healthcare facility.[26]
[d] Urinary tract abnormalities: presence of urinary tract obstruction, urethral strictures, urolithiasis, benign prostatic hypertrophy, congenital abnormalities, or functional problems such as neurogenic bladder or vesicoureteral reflux.
[e] Chronic urinary catheterization was defined as a catheter that had been in place for more than 7 days.[27]

A higher C-reactive protein concentration was more common in the bacteremic group (160.52 ± 106.67% vs. 77.59 ± 74.19, $p < 0.001$). (Table 2).

The significant risk factors that were identified by univariate analysis were further analyzed by multivariate logistic regression. This analysis was able to identify the community source (adjusted odds ratio: 2.70; 95% CI:1.19−6.09; $p = 0.017$), hydronephrosis (adjusted odds ratio: 3.22; 95% CI: 1.24−8.39; $p = 0.017$), WBC band neutrophils accounting for >10% of the WBC count (adjusted odds ratio: 6.09; 95% CI: 2.07−17.94; $p = 0.001$), hyperthermia or hypothermia (adjusted odds ratio: 2.21; 95% CI: 1.01−4.82; $p = 0.047$), and C-reactive protein level >100 mg/L (adjusted odds ratio: 3.11; 95% CI: 1.51−6.39; $p = 0.002$) as independent factors associated with an increased risk of bacteremia in patients with a *P. mirabilis* UTI (Table 3).

Clinical outcomes

Seventeen patients died during their hospitalizations. The in-hospital mortality rate of *P. mirabilis* UTI was 8.9%. Among the 17 patients who died (total), 11 were in the bacteremic group and 6 were in the nonbacteremic group. Univariate analysis showed that a higher mortality rate was significantly associated with *P. mirabilis* bacteremia (16.4% vs. 4.8%, $p = 0.016$), a stay in the ICU (76.5% vs. 27.0%, $p < 0.001$), the occurrence of a shock episode (82.4% vs. 20.1%, $p < 0.001$), vasopressor use (64.7% vs. 18.4%, $p < 0.001$), C-reactive protein concentration >100 mg/dL (70.6% vs. 41.4%, $p = 0.039$), and a body mass index (BMI) <18.0 (47.1% vs. 18.4%, $p = 0.014$). Risk factors identified by univariate analysis were entered into a multivariate logistic regression model, and this analysis identified bacteremia (adjusted odd ratios: 3.52; 95% CI: 1.00−12.40;

Table 2 Laboratory findings and clinical presentation of *P. mirabilis* UTIs, with and without bacteremia

Laboratory findings	No.(%) of Episodes		Odds ratio (95% CI)	*p*-value
	Bacteremic UTI $n = 67$	Non-bactermic UTI $n = 124$		
Body temperature >38°C or <36.0°C	51 (76.1)	70 (56.3)	2.45 (1.26–4.78)	0.011*
MAP (mean, mmHg ± SD)	131.44 ± 33.95	128.42 ± 29.64	—	0.539
Pulse rate (mean, beats/min ± SD)	103.18 ± 24.42	98.97 ± 23.93	—	0.266
Azotemia	39 (58.2)	51 (41.1)	1.99 (1.09–3.65)	0.035*
Creatinine (mg/dL, mean ± SD)	1.59 ± 1.39	1.25 ± 1.21	—	0.081
White blood cell count (10^3/μL, mean ± SD)	16.20 ± 9.21	12.146 ± 5.956	—	0.002
White blood cell count (> 12,000/μL),	43 (64.2)	63 (50.8)	1.74 (0.94–3.19)	0.105
Band >10 %	15 (22.4)	8 (6.5)	4.18 (1.67–10.53)	0.003*
C-reactive protein (mg/L, mean ± SD)	160.52 ± 106.67	77.59 ± 74.19	—	<0.001*

*$p < 0.05$.
Abbreviations: CI, confidence interval; MAP, mean arterial pressure; SD, standard deviation.

*p*v0.049), shock episode (adjusted odds ratio: 9.36; 95% CI: 1.58–55.46; $p = 0.014$), and an extremely low BMI (< 18.0) (adjusted odds ratio: 3.8; 95% CI: 1.12–13.00; $p = 0.033$) as factors associated with a high risk of in-hospital mortality (Table 4).

In vitro antimicrobial resistance profiles

MDR *P. mirabilis* strains were more frequently isolated from the nonbacteremic group than from the bacteremic group (but this finding was not statistically significant [50.0 % vs. 35.8%; $p = 0.084$]). MDR *P. mirabilis* strains were more common in patients with nosocomial infections that were obtained from either a hospital or another healthcare facility ($p < 0.001$) (data not shown). Univariate analysis revealed that the percentage of *P. mirabilis* isolates susceptible to the first-generation application of cephalosporin and fluoroquinolone was significantly lower in the nonbacteremic group (71.8% vs. 88.1%, $p = 0.017$; 58.1% vs. 83.6%, $p = 0.001$, respectively). Carbapenems were fully active *in vitro* in both groups. (Table 5) The percentage of patients who received the appropriate initial antibiotic treatment was smaller in the group infected with MDR strains than in the group infected with non-MDR strains (72.1% vs. 89.5%, $p = 0.004$); however, MDR *P. mirabilis* infection was not associated with a poor clinical outcome (41.2% vs. 45.4%, $p = 0.937$). The bacteremic group was treated with antibiotics for an average of 16.00 ± 6.22 days.

We compared the preadmission histories of both groups. The use of antibiotics before culture collection and the duration of symptoms prior to receiving medical care were recorded. Difference in the use of antimicrobial agents to treat the bacteremic and nonbacteremic groups was of borderline significance (57.9% vs. 42.1%, $p = 0.052$). From the onset of symptoms to the initiation of medical care, the difference in average duration in bacteremic and nonbacteremic groups was not statistically significant (2.29 ± 3.66 vs. 2.00 ± 2.16 days, $p = 0.903$) (Table 1).

Table 3 Multivariate analysis of factors associated with *P. mirabilis* bacteremic urinary tract infections

Variable	Odds ratio	Univariable (95% CI)	*p*-value	Adjusted Odds ratio	Multivariable (95% CI)	*p*-value
Community-acquired	2.51	(1.26–5.00)	0.01	2.70	(1.19–6.09)	0.017*
Hydronephrosis	5.55	(2.69–11.49)	<0.001	3.22	(1.24–8.39)	0.017*
Urolithiasis	2.54	(1.35–4.78)	0.006	1.13	(0.46–2.76)	0.792
Bands >10% of white blood cell count	4.18	(1.67–10.53)	0.003	6.09	(2.07–17.94)	0.001*
Body temperature >38.0°C or <36.0°C	2.45	(1.26–4.78)	0.011	2.21	(1.01–4.82)	0.047*
BUN >20 mg/dL	1.99	(1.09–3.65)	0.035	1.78	(0.88–3.61)	0.111
C-reactive protein >100 mg/L	4.02	(2.14–7.51)	<0.001	3.11	(1.51–6.39)	0.002*

*$p < 0.05$.
Adjusted odds ratio: variables with *p*-values <0.05 were further analyzed for multivariable analysis for logistic regression, yielding the expected 95% CI and adjusted odds ratio.
BUN, blood urea nitrogen; CI, confidence interval.

Table 4 Independent risk factors associated with *P. mirabilis* UTI survival (the odds ratio is for mortality)

Variable	Death ($n = 17$)	Survival ($n = 174$)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	p-value
Age (y)	71.47 ± 18.38	69.83 ± 16.26	0.70	—	—
Sex (female)	10 (58.8)	112 (64.4)	0.79 (0.29–2.18)	—	—
Bacteremia	11 (16.4)	56 (32.21)	3.86 (1.36–10.97)*	3.52 (1.00–12.40)*	0.049*
ICU admission	13 (76.5)	47 (27.0)	8.77 (2.72–28.57)*	1.85 (0.30–11.49)	0.511
Shock	14 (82.4)	35 (20.1)	18.52 (5.05–66.60)*	9.36 (1.58–55.46)*	0.014*
Vasopressor use	11 (64.7)	32 (18.4)	8.13 (2.80–23.80)*	2.00 (0.28–5.60)	0.764
Appropriate initial antimicrobial therapy[a]	14 (82.4)	142 (81.6)	1.18 (0.29–3.88)		
COPD	2 (11.8)	20 (11.5)	1.02 (0.22–4.83)		
Cerebral vascular disease	9 (52.9)	80 (46.0)	1.32 (0.49–3.58)		
Bedridden	14 (82.4)	99 (56.9)	3.53 (0.98–12.80)		
Nosocomial[b]	7 (41.2)	60 (34.5)	1.33 (0.48–3.68)		
Diabetes mellitus	6 (35.3)	55 (31.6)	1.18 (0.40–3.35)		
Hydronephrosis	1 (5.9)	43 (24.7)	0.19 (0.002–1.30)		
Kidney failure[c]	7 (41.1)	40 (22.9)	2.35 (0.75–7.26)		
Urolithiasis	3 (17.6)	57 (32.8)	0.44 (0.12–1.59)		
Chronic urinary catheterization[d]	8 (47.1)	67 (89.3)	1.42 (0.52–3.86)		
C-reactive protein >100 mg/L	12 (70.6)	72 (41.4)	3.40 (1.15–10.10)*	0.78 (0.22–2.81)	0.700
Body temperature >38.0°C or <36°C	9 (52.9)	112 (64.4)	0.62 (0.23–1.69)		
Multidrug resistant isolates[e]	7 (41.2)	79 (45.4)	0.85 (0.36–2.31)		
BMI <18.0	8 (47.1)	32 (18.4)	3.94 (1.41–10.99)*	3.80 (1.12–13.00)*	0.033*

*$p < 0.05$.

Adjust odd ratio: univariables with p-values < 0.05 were further analyzed by multivariable analysis for logistic regression, yielding the expected 95% CI and adjusted odd ratio.

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

[a] Considered appropriate if at least one antimicrobial agent was active *in vitro* according to CLSI guidelines and administrated within 48 hours after all samples were collected for culturing.

[b] Nosocomial infection: (1) infections occurring more than 48 hours after hospital admission or after emergency department admission, or (2) those who were referred from another hospital or healthcare facility.[26]

[c] Kidney failure is defined as a creatinine level >1.5 mg/dL.

[d] When the catheter had been maintained for more than 7 days.

[e] Multidrug resistant isolates are defined as resistant or intermediately susceptible to more than three classes of the flowing antimicrobial groups:[30] (1) ampicillin, amoxicillin/clavulanate, or piperacillin/tazobactam; (2) cefuroxime, ceftriaxone, and cefepime; (3) carbapenems; (4) ciprofloxacin or levofloxacin; (5) gentamicin or amikacin; (6) cotrimoxazole.

Discussion

Our analysis identified independent factors associated with the increased risk of bacteremia in patients with *P. mirabilis* UTIs. These independent risk factors include the following: community-acquired infection, hydronephrosis, the increased presence of band neutrophils accounting for >10% of the WBC count, hyperthermia or hypothermia, and a C-reactive protein level >100 mg/L. In a previous survey, bacteremic UTI s were often associated with longer hospitalizations, more severe complications, and higher mortality rates compared with nonbacteremic UTIs.[31,32] Several studies have surveyed the clinical presentation and laboratory manifestations of bacteremic UTIs. Leibovici et al investigated 247 older patients (median age: 75 years) and found that a high serum creatinine level, high WBC count, hyperthermia, diabetes mellitus, and low serum albumin level are more common in patients with bacteremic UTIs caused by various kinds of pathogens.[32] In contrast, Bahagon et al showed no statistically significant difference between diabetes mellitus, chronic kidney disease (CKD), or immunocompromised status as risk factors for bacteremic UTI, but both of their studies identified severe SIRS reactions as more common in the bacteremic group;[32,33] however, the leading causative pathogen among the patients in these studies was *E. coli*, and their analysis was performed in patients with different pathogens. The risk factors for *P. mirabilis* bacteremic UTI have not been fully elucidated.[17,34,35]

Compared with UTIs caused by *E. coli*, UTIs caused by *Proteus spp.* are often more severe and associated with a higher incidence of pyelonephritis. In *Proteus spp* UTIs, the urine pH is often >7.2. The majority of the bloodstream infections caused by *Proteus spp.* originate from a UTI and are often associated with urinary catheters. Consistent with previous studies,[32,36] our study demonstrates that hydronephrosis, band neutrophils accounting for >10% of the WBC count, hyperthermia or hypothermia, a severe SIRS reaction, and a high C-reactive protein concentration are more common in *P. mirabilis* bacteremic UTIs; however,

Table 5 Antimicrobial sensitivity profiles

Antimicrobial agents	No. (%) of Episodes		Odd ratio (95% CI)	*p*-value
	Bacteremic UTI $n = 67$	Non-bacteremic UTI $n = 124$		
Cephalosporins				
First generation	59 (88.1)	89 (71.8)	2.90 (1.26—6.67)	0.017*
Second generation[a]	63 (94.0%)	103 (83.1%)	3.22 (1.05—9.80)	0.055
Third generation[b]	59 (88.1%)	95 (76.6)	2.25 (0.96—5.26)	0.086
Fourth generation[c]	59 (88.1%)	95 (76.6)	2.25 (0.96—5.26)	0.086
Extended penicillin[d]	26 (38.8)	36 (29.0)	1.550 (0.83—2.90)	0.224
Cotrimoxazole	23 (34.3)	36 (29.0)	1.28 (0.68—2.42)	0.554
Aminoglycoside[e]	46 (68.7)	66 (53.2)	1.93 (1.03—3.60)	0.056
Carbapenem[f]	67 (100)	124 (100)	—	—
Fluoroquinolone[g]	56 (83.6)	72 (58.1)	3.68 (1.76—7.69)	0.001*
Multidrug- resistant isolates[h]	24 (35.8)	62 (50.0)	1.79 (0.97—3.30)	0.084

[a] Second-generation cephalosporin: cefuroxime or cefmetazole.
[b] Third-generation cephalosporin: ceftriaxone or ceftazidime.
[c] Fourth-generation cephalosporin: cefepime.
[d] Extended penicillin: ampicillin, amoxicillin/clavulanate, or piperacillin/tazobactam.
[e] Aminoglycoside: gentamicin or amikacin.
[f] Carbapenem: imipenem/meropenem/ertapenem.
[g] Fluoroquinolone: ciprofloxacin or levofloxacin.
[h] Multidrug-resistant isolates are defined as resistance or intermediate susceptibility to more than three classes of the following antimicrobial groups:[30] (1) ampicillin, amoxicillin/clavulanate, or piperacillin/tazobactam; (2) cefuroxime, ceftriaxone, or cefepime; (3) carbapepenems; (4) ciprofloxacin or levofloxacin; (5) gentamicin or amikacin; (6) cotrimoxazole.

there was no statistically significant difference in terms of diabetes mellitus, chronic obstructive pulmonary disease (COPD), or immunocompromised status. Furthermore, our results show that bacteremic *P. mirabilis* UTIs are more common in patients with community-acquired infections. Preadmission history of antimicrobial treatments and duration of symptoms prior to the onset of medical care of both groups were investigated, but no statistically significant difference was confirmed. In contrast, higher rates of urolithiasis and hydronephrosis were noted in patients with community-acquired infections in our cohort. At the same time, a lower proportion of chronic urinary catheterization was also noted in the community-acquired group. Thus, patients with functional urological problems, such as neurogenic bladder or urinary retention, are at a higher risk of developing hydronephrosis and urolithiasis formation and encrustation. Encrustation further blocks the lumen, obstructs flow, and causes vesicoureteral reflux, thereby inducing an ascending infection that can further develop into pyelonephritis, bacteremia, and shock. This may explain why the bacteremic *P. mirabilis* UTIs are more common in patients with community-acquired infections.

In our study, 17 patients died (8.9%), 11 of whom were in the bacteremic group and 6 of whom were in the non-bacteremic group. Multivariate analysis using logistic regression showed that bacteremic UTI, shock, and an extremely low BMI are independent risk factors of mortality. In our study, patients with *P. mirabilis* bacteremia had a higher rate of mortality than nonbacteremic patients. This finding is similar to findings in other studies on *Enterobacteriaceae*-causing bacteremic UTIs.[18,36] Two previous studies have pointed out that bacteremic UTI in patients with a low serum albumin level and a severe SIRS reaction tended to be associated with poor clinical outcomes.[28,36] Our finding that an extremely low BMI is an independent risk factor for poor clinical outcomes has also been reported in previous studies.[37,38] The reason why we did not investigate an association between the serum albumin level and clinical outcome was because of missing clinical data from some of our patients. Our results show that an extremely low BMI is similar to a low serum albumin level in terms of its usefulness as a predictor of a poor clinical outcome. Sometimes a low BMI is superior to albumin as a clinical predictor because BMI may be more readily determined by primary care clinicians.

Our study demonstrates that isolates of *P. mirabilis* in nonbacteremic UTIs are less susceptible to first-generation cephalosporin and fluoroquinolone than isolates of *P. mirabilis* in bacteremic UTIs. In comparison with non-MDR isolates, more patients infected with MDR strains did not receive the appropriate initial antibiotic treatment; however, MDR *P. mirabilis* infections were not associated with poor clinical outcomes (Table 4), and this finding has been noted in other studies.[30,39] Endimiani et al reported that ESBL-producing *P. mirabilis* bloodstream infections are associated with poor outcomes.[28] Differences between these results may be because MDR *P. mirabilis* isolates were less common in the bacteremic group in our cohort.

The most important limitation of this study is that the number of cases was small. Another limitation is that our study is a retrospective study, and the preadmission histories of each patient (such as the classes of antibiotics used before and during treatment) were based primarily on statements provided by the patients and their families and are, therefore, difficult to interpret. Finally, missing data on serum albumin levels in some of our patients led to

difficulty evaluating the association between serum albumin levels and patient's clinical outcome.

In conclusion, the independent risk factors for bacteremia-complicating *P. mirabilis* UTIs were determined to be the following: community-acquired infection, hydronephrosis, SIRS reaction, band neutrophils accounting for >10% of the WBC count, and a high C-reactive protein level. Bacteremic UTIs, shock, and low BMI were associated with poor clinical outcomes. We recommend that patients with the clinical presentation and risks factors mentioned above undergo further radiologic imaging studies, such as abdominal sonography or a CT scan. Further studies that include a greater number of cases may be necessary.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to the manuscript that is being submitted to the *Journal of Microbiology, Immunology and Infection*.

References

1. Mobley HL, Belas R. Swarming and pathogenicity of *Proteus mirabilis* in the urinary tract. *Trends Microbiol* 1995;**3**:280—4.
2. Pearson MM, Sebaihia M, Churcher C, Quail MA, Seshasayee AS, Luscombe NM, et al. Complete genome sequence of uropathogenic *Proteus mirabilis*: a master of both adherence and motility. *J Bacteriol* 2008;**190**:4027—37.
3. Harrison LH, Cass AS, Bullock BC, Cox CE. Experimental pyelonephritis in dogs: confirmation by antibody response. *J Urol* 1973;**109**:163—6.
4. Warren JW, Tenney JH, Hoopes JM, Muncie HL, Anthony WC. A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. *J Infect Dis* 1982;**146**: 719—23.
5. Broomfield RJ, Morgan SD, Khan A, Stickler DJ. Crystalline bacterial biofilm formation on urinary catheters by urease-producing urinary tract pathogens: a simple method of control. *J Med Microbiol* 2009;**58**:1367—75.
6. Kunin CM. Blockage of urinary catheters: role of microorganisms and constituents of the urine on formation of encrustations. *J Clin Epidemiol* 1989;**42**:835—42.
7. Thornsberry C, Yee YC. Comparative activity of eight antimicrobial agents against clinical bacterial isolates from the United States, measured by two methods. *Am J Med* 1996;**100**: 26S—38S.
8. Karlowsky JA, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Trends in antimicrobial susceptibilities among *Enterobacteriaceae* isolated from hospitalized patients in the United States from 1998 to 2001. *Antimicrob Agents Chemother* 2003; **47**:1672—80.
9. Lockhart SR, Abramson MA, Beekmann SE, Gallagher G, Riedel S, Diekema DJ, et al. Antimicrobial resistance among Gram-negative bacilli causing infections in intensive care unit patients in the United States between 1993 and 2004. *J Clin Microbiol* 2007;**45**:3352—9.
10. Giamarellos-Bourboulis EJ, Papadimitriou E, Galanakis N, Antonopoulou A, Tsaganos T, Kanellakopoulou K, et al. Multidrug resistance to antimicrobials as a predominant factor influencing patient survival. *Int J Antimicrob Agents* 2006;**27**: 476—81.
11. Endimiani A, Luzzaro F, Perilli M, Lombardi G, Colì A, Tamborini A, et al. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment outcome of patients receiving imipenem or ciprofloxacin. *Clin Infect Dis* 2004;**38**:243—51.
12. Kim YK, Pai H, Lee HJ, Park SE, Choi EH, Kim J, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;**46**:1481—91.
13. Menashe G, Borer A, Yagupsky P, Peled N, Gilad J, Fraser D, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing *Enterobacteriaceae* isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;**33**:188—93.
14. Wong-Beringer A, Hindler J, Loeloff M, Queenan AM, Lee N, Pegues DA, et al. Molecular correlation for the treatment outcomes in bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* with reduced susceptibility to ceftazidime. *Clin Infect Dis* 2002;**34**:135—46.
15. Diekema DJ, Pfaller MA, Jones RN, Doern GV, Kugler KC, Beach ML, et al. Trends in antimicrobial susceptibility of bacterial pathogens isolated from patients with bloodstream infections in the USA, Canada and Latin America. SENTRY Participants Group. *Int J Antimicrob Agents* 2000; **13**:257—71.
16. Luzzaro F, Viganò EF, Fossati D, Grossi A, Sala A, Sturla C, et al. Prevalence and drug susceptibility of pathogens causing bloodstream infections in northern Italy: a two-year study in 16 hospitals. *Eur J Clin Microbiol Infect Dis* 2002;**21**:849—55.
17. Kim BN, Kim NJ, Kim MN, Kim YS, Woo JH, Ryu J. Bacteraemia due to tribe *Proteeae*: a review of 132 cases during a decade (1991-2000). *Scand J Infect Dis* 2003;**35**:98—103.
18. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000;**26**(Suppl. 1):S64—74.
19. Pittet D, Rangel-Frausto S, Li N, Tarara D, Costigan M, Rempe L, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU. *Intensive Care Med* 1995;**21**: 302—9.
20. Tal S, Guller V, Levi S, Bardenstein R, Berger D, Gurevich I, et al. Profile and prognosis of febrile elderly patients with bacteremic urinary tract infection. *J Infect* 2005;**50**:296—305.
21. Al-Hasan MN, Eckel-Passow JE, Baddour LM. Bacteremia complicating gram-negative urinary tract infections: a population-based study. *J Infect* 2010;**60**:278—85.
22. Barkham TM, Martin FC, Eykyn SJ. Delay in the diagnosis of bacteraemic urinary tract infection in elderly patients. *Age Ageing* 1996;**25**:130—2.
23. van Nieuwkoop C, Hoppe BP, Bonten TN, Van't Wout JW, Aarts NJ, Mertens BJ, et al. Predicting the need for radiologic imaging in adults with febrile urinary tract infection. *Clin Infect Dis* 2010;**51**:1266—72.
24. Velasco M, Martinez JA, Moreno-Martinez A, Horcajada JP, Ruiz J, Barranco M, et al. Blood cultures for women with uncomplicated acute pyelonephritis: are they necessary? *Clin Infect Dis* 2003;**37**:1127—30.
25. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. *Methods Inf Med* 1993;**32**:382—7.
26. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309—32.
27. Chin BS, Kim MS, Han SH, Shin SY, Choi HK, Chae YT, et al. Risk factors of all-cause in-hospital mortality among Korean elderly bacteremic urinary tract infection (UTI) patients. *Arch Gerontol Geriatr* 2011;**52**:e50—5.
28. Endimiani A, Luzzaro F, Brigante G, Perilli M, Lombardi G, Amicosante G, et al. *Proteus mirabilis* bloodstream infections: risk factors and treatment outcome related to the expression

of extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2005;**49**:2598—605.
29. National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial susceptibility testing, 18th informational supplement. NCCLS document M100—S18*. Wayne, PA: National Committee for Clinical Laboratory Standards; 2008.
30. Cohen-Nahum K, Saidel-Odes L, Riesenberg K, Schlaeffer F, Borer A. Urinary tract infections caused by multi-drug resistant *Proteus mirabilis*: risk factors and clinical outcomes. *Infection* 2010;**38**:41—6.
31. Jerkeman M, Braconier JH. Bacteremic and non-bacteremic febrile urinary tract infection: a review of 168 hospital-treated patients. *Infection* 1992;**20**:143—5.
32. Leibovici L, Greenshtain S, Cohen O, Wysenbeek AJ. Toward improved empiric management of moderate to severe urinary tract infections. *Arch Intern Med* 1992;**152**:2481—6.
33. Bahagon Y, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM. Prevalence and predictive features of bacteremic urinary tract infection in emergency department patients. *Eur J Clin Microbiol Infect Dis* 2007;**26**:349—52.
34. Berger SA. *Proteus* bacteraemia in a general hospital 1972-1982. *J Hosp Infect* 1985;**6**:293—8.
35. Watanakunakorn C, Perni SC. *Proteus mirabilis* bacteremia: a review of 176 cases during 1980-1992. *Scand J Infect Dis* 1994;**26**:361—7.
36. Hsu CY, Fang HC, Chou KJ, Chen CL, Lee PT, Chung HM. The clinical impact of bacteremia in complicated acute pyelonephritis. *Am J Med Sci* 2006;**332**:175—80.
37. Le Blanc K, Ringdén O, Remberger M. A low body mass index is correlated with poor survival after allogeneic stem cell transplantation. *Haematologica* 2003;**88**:1044—52.
38. Lin YF, Ko WJ, Chu TS, Chen YS, Wu VC, Chen YM, et al. The 90-day mortality and the subsequent renal recovery in critically ill surgical patients requiring acute renal replacement therapy. *Am J Surg* 2009;**198**:325—32.
39. Yang YS, Ku CH, Lin JC, Shang ST, Chiu CH, Yeh KM, et al. Impact of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* on the outcome of community-onset bacteremic urinary tract infections. *J Microbiol Immunol Infect* 2010;**43**:194—9.