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Letters to the Editor

## Risk factors for mortality and clinical implications of catheter-related infections in patients with bacteraemia caused by *Stenotrophomonas maltophilia*☆

Sir,

*Stenotrophomonas maltophilia* is a non-fermentative Gram-negative bacillus, previously known as *Pseudomonas maltophilia* and later as *Xanthomonas maltophilia* [1]. *Stenotrophomonas maltophilia* has emerged as an important cause of morbidity and mortality in hospitalised patients [2]. Despite its low virulence, therapy for infections with this pathogen is challenging because of its intrinsic resistance to most antimicrobial agents [3]. Hospital mortality associated with *S. maltophilia* bacteraemia (SMB) is reported to be >20%. There have been some studies on mortality of SMB, but most studies included only small numbers of patients [4,5]. Furthermore, data regarding risk factors for mortality of SMB are limited.

Thus, in the present study we describe a recent 7-year survey of SMB and the clinicoepidemiological features of patients with SMB. This study was conducted to identify the risk factors for mortality and to evaluate the effect of catheter-related infection (CRI) on outcome in patients with SMB.

Patients were included in the study if blood culture results were positive for *S. maltophilia* from January 1999 to December 2006 at Samsung Medical Center, Seoul, Republic of Korea, a 1350-bed tertiary-care university hospital. Only the first bacteraemic episode for each patient was included in the analysis. A retrospective observational cohort study was conducted. The medical records of patients were reviewed and data were collected, including age, gender, underlying disease, site of infection and severity of illness (as calculated by Pitt bacteraemia score and Charlson's weighted index of morbidity). The main outcome measure used was the 30-day mortality rate. SMB was defined as a finding of *S. maltophilia* in a blood culture specimen. Clinically significant bacteraemia was defined as at least one positive blood culture together with clinical features compatible with systemic inflammatory response syndrome. According to the management guidelines of the Infectious Diseases Society of America, bacteraemia was considered as definite CRI if there was no apparent source of bacteraemia except the central venous catheter (CVC) and if the same organism was isolated from semiquantitative cultures (>15 colony-forming units) of the CVC tip and from positive peripheral blood cultures. Possible CRI was indicated by the finding of a positive blood culture with no other apparent source of bacteraemia except the catheter. During the study period, a total of 112 patients were identified. Among these patients, a total of 109 patients with SMB were enrolled. Three patients were excluded from the analysis because they were transferred to another hospital and their outcome was not evaluable. The demographic and clinical features of the patients are given in Table 1. Regarding the primary site of infection, the most common primary site was CRI ($n = 47$; 43.1%). Among the 47 CRI patients, 38 patients had definite CRI and 9 patients had possible CRI. The resistance rates of the *S. maltophilia* blood isolates to levofloxacin, trimethoprim/sulfamethoxazole, ceftazidime and ticarcillin/clavulanic acid were 15.0%, 5.5%, 43.3% and 24.8%, respectively. The overall 30-day mortality rate for SMB was 26.6% (29/109). Multivariate analysis using a logistic regression model including the variables associated with mortality by univariate analysis ($P < 0.05$) showed that the significant independent risk factors for mortality were prolonged hospitalisation (≥30 days prior to bacteraemia), high Pitt bacteraemia score and Intensive Care Unit (ICU)-onset bacteraemia (Table 1). CRI was found to be a protective factor for mortality (odds ratio 0.19, 95% confidence interval 0.04–0.87; $P = 0.032$). The mortality rate was significantly higher for non-CRI than for CRI (37.1% vs. 12.8%; $P = 0.005$). Among the 47 patients with CRI, 44 patients (93.6%) received antimicrobial therapy and underwent catheter removal.

Previous studies associated shock, nosocomial bacteraemia, long-lasting neutropenia, respiratory tract origin, thrombocytopenia and inappropriate therapy with increased mortality of SMB, whilst CRI was associated with a favourable prognosis [4,6]. Our study augmented the findings of previous work. We additionally found that prolonged hospitalisation (≥30 days prior to bacteraemia), high Pitt bacteraemia score (≥4) and ICU-onset bacteraemia were strong prognostic factors of mortality. Shock was included in the Pitt bacteraemia score calculations. Non-CRI patients had significantly higher mortality rates than the CRI patients; furthermore, after adjusting for confounding variables, multivariate analyses identified CRI as an independent protective predictor for mortality. Most previous studies had analysed a small population, therefore we analysed a relatively large population of patients with SMB. The incidence of intravascular catheter-related bloodstream infection due to Gram-negative bacilli may be on the rise [7]; in particular, CVCs are the most common source of non-fermentative Gram-negative bacteraemia, with *S. maltophilia* being one of the most commonly isolated organisms [6].

In conclusion, we found that CRI was the most frequent source for SMB but that CRI was a protective factor for mortality. Clinicians must be aware of the probability of CRI causing SMB and consider the necessity of removal of the catheter in addition to appropriate antibiotic therapy, which may decrease the mortality of SMB. Future studies are warranted to evaluate whether catheter removal is essential in the treatment of SMB.

☆ This study was presented in part at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 17–20 September 2007, Chicago, IL (abstract 2761).

**Table 1**
Risk factors associated with 30-day mortality in *Stenotrophomonas maltophilia* bacteraemia[a]

| Variable | Total ($n = 109$) | No. of survivors ($n = 80$) | No. of non-survivors ($n = 29$) | Univariate analysis ($P$-value)[b] | Multivariate analysis[c] | |
|---|---|---|---|---|---|---|
| | | | | | Odds ratio (95% CI) | $P$-value |
| Gender (M/F) | 77/32 (70.6/29.4) | 57/23 (71.3/28.8) | 20/9 (69.0/31.0) | 0.220 | | |
| Age (years) (mean ± S.D.) | 52.9 ± 15.4 | 52.1 ± 15.7 | 55.8 ± 14.7 | 0.813 | | |
| Underlying malignancy | 88 (80.7) | 62 (77.5) | 26 (89.7) | 0.155 | | |
| Immunocompromised host | 45 (41.3) | 31 (38.8) | 14 (48.3) | 0.372 | | |
| ≥30 days hospital stay prior to bacteraemia onset | 29 (26.6) | 14 (17.5) | 15 (51.7) | 0.001 | 5.45 (1.48–20.10) | 0.011 |
| Infection site | | | | | | |
| CRI | 47 (43.1) | 41 (51.3) | 6 (20.7) | 0.005 | 0.19 (0.04–0.87) | 0.032 |
| Pneumonia | 24 (22.0) | 13 (16.3) | 11 (37.9) | 0.035 | | |
| IAI | 22 (20.2) | 14 (17.5) | 8 (27.6) | 0.206 | | |
| SSTI | 7 (6.4) | 5 (6.3) | 2 (6.9) | 1.000 | | |
| UTI | 2 (1.8) | 1 (1.3) | 1 (3.4) | 0.470 | | |
| Others | 7 (6.4) | 6 (7.5) | 1 (3.4) | 0.671 | | |
| Pitt bacteraemia score | | | | | | |
| 0–3 | 82 (75.2) | 66 (82.5) | 16 (55.2) | | | |
| ≥4 | 27 (24.8) | 14 (17.5) | 13 (44.8) | 0.006 | 3.53 (1.06–11.79) | 0.040 |
| Charlson's WIC | | | | | | |
| 0–2 | 86 (78.9) | 68 (85.0) | 18 (62.1) | | | |
| ≥3 | 23 (21.1) | 12 (15.0) | 11 (37.9) | 0.016 | | |
| ICU stay during bacteraemia | 25 (22.9) | 11 (13.8) | 14 (48.3) | 0.001 | 24.87 (2.98–207.30) | 0.003 |
| On mechanical ventilator | 18 (16.5) | 8 (10.0) | 10 (34.5) | 0.007 | | |
| Indwelling CVC during bacteraemia | 83 (76.1) | 59 (73.8) | 24 (82.8) | 0.768 | | |

CI, confidence interval; S.D., standard deviation; CRI, catheter-related infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection; UTI, urinary tract infection; WIC, weighted index of morbidity; ICU, intensive care unit; CVC, central venous catheter.

[a] Data indicate no. (%) of patients, unless otherwise indicated.

[b] Student's $t$-test was used to compare continuous variables, and $\chi^2$ or Fisher's exact test was used to compare categorical variables.

[c] Variables with $P$-values of <0.05 in the univariate analyses were candidates for multivariate analysis. A stepwise logistic regression analysis was used.

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## Emergence of *Serratia liquefaciens* and *Klebsiella oxytoca* with metallo-β-lactamase-encoding IncW plasmids: further spread of the $bla_{VIM-1}$-carrying integron In-e541

Sir,

VIM-1-producing *Klebsiella pneumoniae* has been established in Greek hospitals [1]. Sporadic isolation of other VIM-1-producing enterobacterial species has also been reported [2,3]. Integron In-e541 ($bla_{VIM-1}$, *aacA7*, *dhfrI* and *aadA*; GenBank accession no. AY340637) is prevalent among these strains. In-e541 is linked with a distinct IncN plasmid type [1]. It is shown here that In-e541 has been acquired by an IncW plasmid from *Serratia liquefaciens* and *Klebsiella oxytoca*.

*Serratia liquefaciens* E815 and *K. oxytoca* E912 were isolated in 2007 from patients in Evgenidion Hospital, Athens, Greece. β-Lactam minimum inhibitory concentrations (MICs) were determined by agar dilution. Susceptibility to other drugs was evaluated by disk diffusion. Metallo-β-lactamase (MBL) production was tested by the double-disk synergy test (DDST) with imipenem and ethylene diamine tetra-acetic acid (EDTA). Detection of extended-spectrum β-lactamases (ESBLs) was performed using the DDST combining amoxicillin/clavulanic acid with oxyimino-β-lactams.

Conjugation experiments were performed in broth cultures using a rifampicin-resistant *Escherichia coli* K12 strain as recipient. Transconjugants were selected with rifampicin (300 mg/L) plus ampicillin (40 mg/L). Plasmid DNA prepared with a QIAGEN Plasmid Midi Kit was used to transform *E. coli* DH5α. Transformants were selected using ampicillin (40 mg/L). Plasmid incompatibility groups were determined by a polymerase chain reaction (PCR)-based typing method [4], and sequencing of the respective amplicons. Restriction fragment length polymorphism (RFLP) and hybridisation with a $bla_{VIM-1}$-specific probe were also performed [5]. PCRs specific for $bla_{VIM}$ and $bla_{SHV}$ as well as segments of class 1 integrons and IS*26* have been described previously [2,5,6].

β-Lactamase extracts were obtained by ultrasonic treatment of broth cultures and were analysed by isoelectric focusing (IEF). Imipenem hydrolysis rates and the inhibitory activity of EDTA were determined by spectrophotometry [5].

Both clinical isolates were non-susceptible to penicillin/inhibitor combinations, cefoxitin, oxyimino-cephalosporins, aztreonam and carbapenems as well as to ciprofloxacin, trimethoprim/sulfamethoxazole (SXT) and aminoglycosides (Table 1). Both isolates were MBL-positive by the DDST. In the ESBL-detecting DDST, a clear synergy image was observed in *S. liquefaciens* E815 between clavulanic acid and aztreonam. A synergy between the latter two compounds was also seen with *K. oxytoca* E912.

$bla_{VIM-1}$ PCR assays and sequencing of the products showed that both isolates carried $bla_{VIM-1}$. *Serratia liquefaciens* was also $bla_{SHV}$-positive. Sequencing of the respective product indicated that the gene was of the $bla_{SHV-5/12}$ type. Results of IEF experiments were in line with those of PCR. Overlay of IEF gels with $ZnSO_4$ (1 mM) allowed visualisation of β-lactamase bands focusing at a pH of ca. 5.1 as VIM-1 in both isolates. *Serratia liquefaciens* also produced a β-lactamase with an isoelectric point (pI) of 8.2 consistent with SHV-5. A β-lactamase with a pI of 7.3 in the extracts of *K. oxytoca* likely represented the chromosomal OXY enzyme. Clinical isolates exhibited similar imipenem-hydrolysing activities (Table 1) inhibited by EDTA, confirming MBL production. Resistance of *S. liquefaciens* to aztreonam (an unfavourable substrate for VIM-1) was due to the SHV ESBL. Aztreonam-resistant *K. oxytoca* strains commonly overproduce the intrinsic OXY β-lactamase. Co-production of VIM-1 in *K. oxytoca* E912 did not allow a direct comparison of OXY production with that of aztreonam-susceptible *K. oxytoca* isolates. Nevertheless, the promoter sequence of $bla_{OXY}$ in *K. oxytoca* E912