

Independent Predictors for Mortality in Patients with Positive *Stenotrophomonas maltophilia* Cultures†

Andrea LH Kwa,¹PharmD, Jenny GH Low,²MBBS, Tze-Peng Lim,¹BSc (Pharm) Hon, Pay-Chin Leow,¹BSc (Pharm) Hon, Asok Kurup,²MBBS, Vincent H Tam,³PharmD

Abstract

Introduction: *Stenotrophomonas maltophilia* is an emerging pathogen in nosocomial infections that may result in high mortality. *S. maltophilia* often present as part of a polymicrobial culture and it is not well established when treatment is indicated. We aimed to identify predictors of mortality in patients with positive cultures of *S. maltophilia*. **Materials and Methods:** A retrospective cohort study in a tertiary care medical centre was performed in 150 adult patients with positive cultures of *S. maltophilia*. Patients' demographics, underlying diseases, severity of illness, length of hospitalisation, prior antibiotic exposure, number/types of indwelling catheters, culture sites, and appropriateness of empiric therapy were collected. Logistic regression was used to determine the independent risk factor(s) for infection-attributed mortality. **Results:** Ninety-nine males and 51 females were studied. The mean (SD) age and APACHE II score of the patients were 61.9 (16.0) and 14.0 (6.1), respectively. The respiratory tract was the most frequent site (55.3%) where *S. maltophilia* was isolated. Infection-attributed mortality was observed in 22 of the 150 patients (14.7 %). Admission to ICU [Odds ratio (OR), 3.767; 95% confidence interval (CI), 1.277-11.116, $P = 0.016$], and delayed effective treatment (OR, 18.684; 95% CI, 4.050-86.188; $P < 0.001$) were identified as independent risk factors for mortality. **Conclusions:** Predictors of mortality in patients with positive cultures of *S. maltophilia* were identified, which may guide clinicians in patient assessment and devising therapeutic decisions. Further studies are needed to validate our results.

Ann Acad Med Singapore 2008;37:826-30

Key words: Outcomes, Predictors, *Stenotrophomonas maltophilia*

Introduction

Stenotrophomonas (formally *Pseudomonas* or *Xanthomonas*) *maltophilia* is a gram-negative bacillus emerging as an opportunistic, nosocomial pathogen associated with a high mortality rate.^{1,2} Although it was previously considered to have limited pathogenicity, recent reports suggested that infection with *S. maltophilia* was associated with significant morbidity and mortality, particularly in severely immunocompromised and clinically debilitated patients.³ However, many patients with *S. maltophilia* infection have significant underlying illness, and the high clinical failure rate may have been due to the lack of adequate empiric coverage for *S. maltophilia*. Consequently, mortality directly attributed to *S. maltophilia*

infection remains unclear. *S. maltophilia* infection may manifest clinically as bacteraemia, endocarditis, pneumonia, mastoiditis, peritonitis and meningitis.² The risk factors for *S. maltophilia* infection have been reported to be intensive care unit (ICU) admission, mechanical ventilation, immune deficiency, malignancy, cystic fibrosis, neutropaenia, presence of central venous catheters, prolonged hospitalisation, previous therapy with broad spectrum antibiotics and debilitation.²

Clinicians may face a dilemma when a positive culture of *S. maltophilia* is encountered. Clinically it may not be easy to differentiate colonisers from pathogens, and isolation of *S. maltophilia* as part of a polymicrobial culture may make the decision to initiate therapy difficult. Overlooking an

¹ Department of Pharmacy, Singapore General Hospital, Singapore

² Department of Internal Medicine, Division of Infectious Diseases, Singapore General Hospital, Singapore

³ University of Houston College of Pharmacy, Houston, Texas

Address for Correspondence: Andrea LH Kwa, Department of Pharmacy, Block 8 Level 2, Singapore General Hospital, Outram Road, Singapore 169608.

Email: andrea.kwa.l.h@sgh.com.sg

† Poster presentation at the 46th ICAAC in San Francisco, California, USA from 27 to 30 September 2006.

active infection may result in delayed treatment and suboptimal patient outcomes. On the other hand, indiscriminate treatment of all positive cultures may result in overuse of antibiotics and resistance development.⁴ This is especially concerning as efficacious antibiotics to treat *S. maltophilia* infections are limited. Consequently, an early stratification to identify patients at high risk for mortality when they present with a positive culture of *S. maltophilia* may guide clinical evaluation of this patient cohort. Identification of risk factors for mortality in patients with *S. maltophilia* infection early in the course of the disease may also facilitate maximising therapeutic efforts selectively in these patients. The objective of the study was to identify predictors of mortality in patients with positive cultures of *S. maltophilia*.

Materials and Methods

A retrospective cohort study was performed in adult (greater than 18 years of age) patients of Singapore General Hospital (SGH), Singapore with documented positive cultures of *S. maltophilia*. This study was reviewed and approved by the Institution Review Board of the hospital. From 1 January 2003 to 31 December 2005, 300 patients with positive cultures of *S. maltophilia* were identified from microbiology laboratory SGH. One hundred and ninety cases were retrievable from Medical Record Office, SGH, while the rest were not. Out of these 190 cases, 40 cases were rejected as the medical case notes were incomplete. Hence, only 150 cases were analysed.

Pertinent information [e.g. demographics, cultures sources and their susceptibilities, duration of hospital (and ICU if applicable) stay prior to positive culture and after initiation of treatment, presence of chronic diseases (i.e. diabetes mellitus, hypertension, neurological/cardiovascular/pulmonary/gastrointestinal/hepato-splenic/renal/endocrine diseases or malignancies), prior surgery, number and type of indwelling catheters (including intravenous lines, urinary catheters and surgical drainages), concomitant infections, presence of neutropaenia (defined as absolute neutrophil count $<500/\text{mm}^3$), prior antibiotics use within 2 weeks, etc.] were retrieved from the medical case records. For patients with multiple admissions with positive *S. maltophilia* cultures, only data of the first admission were included in the analysis. Patients' severities of illness were assessed by the APACHE (acute physiology and chronic health evaluation) II score on the first day of positive culture. Delayed effective therapy was defined as failure to use an antimicrobial agent exhibiting in vitro activity (and at the appropriate dose adjusted for end organ function) against *S. maltophilia* within the first 48 hours of the first positive culture. Clinically active *S. maltophilia* infections were assessed and diagnosed by an infectious diseases specialist based on: (a) positive culture(s) from

sterile site(s) (i.e. blood or cerebrospinal fluid),⁵ or (b) continual clinical symptoms of infection despite being treated appropriately for all other pathogens except *S. maltophilia* and documented microbiologic eradication of all other pathogens. The primary outcome of the study was infection-attributed mortality (i.e. death related to *S. maltophilia* infection), as assessed independently by two investigators. Infection-attributed mortality (i.e. death related to *S. maltophilia* infection) was defined as persistent clinical active *S. maltophilia* infection (defined above), supported by positive *S. maltophilia* cultures from the same site within 48 hours of demise (with no other positive cultures), and based on the clinical judgment of infectious diseases specialists. Infection-attributed mortality was preferred to all-cause (crude) mortality since mortality due other causes (e.g. cardiovascular event or underlying malignancy) would have been ruled out. All-cause (crude) mortality was in-hospital mortality in our study.

Logistic regression was used to explore various risk factors associated with infection-attributed mortality. Univariate analyses were performed separately for each variable to ascertain the relative risk (RR) and 95% confidence interval (CI). Variables with *P* values of <0.05 and high relative risks in the univariate analysis were subsequently included in the logistic regression model for the multivariate analysis. Forward selection processes were utilised. A *P* value of ≤ 0.05 was considered statistically significant unless stated otherwise. All statistical analyses were performed using the SPSS program version 12.0 (SPSS Inc., Chicago, IL). The study had no external funding source.

Results

One hundred and fifty patients with positive cultures of *S. maltophilia* were identified between January 2003 and February 2006. Demographics and the clinical characteristics of the patients are summarised in Table 1. Polymicrobial cultures (concurrent with *S. maltophilia*) were common and included 37 (24.7%) methicillin-resistant *Staphylococcus aureus*, 33 (22.0%) *Enterococcus* sp., 35 (23.3%) *Pseudomonas aeruginosa*, 33 (22.0%) *Acinetobacter baumannii*, 26 (17.3%) *Klebsiella* sp. and 14 (9.3%) *Escherichia coli*. Fifty-six patients (37.7%) had monomicrobial cultures of *S. maltophilia* from 1 culture site, while 94 (62.3%) patients had polymicrobial cultures from 1 culture site. Sixty patients (40.0%) were thought to have clinically active infections due to *S. maltophilia*. All-cause (crude) and infection-attributed mortality due to *S. maltophilia* were found in 49 (32.7%) and 22 (14.7%) patients, respectively. In the 22 patients who died of *S. maltophilia* infection, 2 patients received effective treatment within 48 hours, 12 patients received delayed treatment and 8 patients did not receive any treatment. Concomitant

Table 1. Patients' Demographics and Clinical Characteristics*

Age (y)	61.9 ± 16.0 (15-89)
Gender (Male/Female)	99/51
Comorbidities	
None	12
1-2	56
(≥3)	82
APACHE II Score	14.0 ± 6.1 (0-38)
Admission to ICU	46
Length of hospitalisation prior to positive culture (days)	12.2 ± 14.4 (0-120)
Number of indwelling catheters	3.2 ± 2.3 (0-9)
Neutropenia (<500 cells/mm ³)	13
Prior surgery	66
Culture sites of <i>S. maltophilia</i>	
Respiratory tract	83
Blood (peripheral)	17
Blood (central catheter)	5
Urine	22
Wound	17
Others	15
Number of patients who received treatment	42

ICU: intensive care unit

*mean ± standard deviation (range)

infections (such as due to *P. aeruginosa* or methicillin-resistant *S. aureus*) were treated appropriately and microbiologic eradication of these pathogens was documented.

The independent predictors of infection-attributed mortality due to *S. maltophilia* in the univariate analysis are shown in Table 2. ICU admission, previous therapy with piperacillin-tazobactam and delayed effective treatment variables were the only variables used for multivariate analysis. In the multivariate analysis, ICU admission and delayed effective treatment for *S. maltophilia* were the only independent factors found to be associated with infection-attributed mortality (Table 2).

Discussion

S. maltophilia has become an important nosocomial pathogen in debilitated patients,⁶ mortality rate was reported to be as high as 36.5% to 45.4%.^{2,7} Mortality due to *S. maltophilia* infection may be difficult to assess due to patient's comorbidities. No study to date has systematically evaluated the risk factors for attributed mortality due to *S. maltophilia* infection. Previous studies have reported attributed mortality rates of *S. maltophilia* bacteraemia, which ranged from 12.5% to 41%.⁸⁻¹² We found an infection-attributed mortality of 14.7% in our patient cohort and 36.7% among patients deemed to be infected with *S. maltophilia*, but our study did not specify site of infection. Bacteraemia being a more aggressive stage of infection may have accounted for the higher mortality rates reported.

Table 2. Logistic Regression Analysis for Infection-attributed Mortality due to *S. maltophilia*

Variables	Univariate analysis		Multivariate analysis	
	RR (95% CI)	P	OR (95% CI)	P
Length of hospitalisation	1.014 (1.002-1.027)	0.025		
Admission to ICU*	6.703 (2.506-17.933)	<0.001	3.767 (1.277-11.116)	0.016
Length of stay in ICU	1.064 (1.028-1.101)	<0.001		
Pulmonary disease	2.407 (0.957-6.054)	0.062		
Endocrine/gastrointestinal disease	2.738 (1.092 - 6.870)	0.032		
Number of indwelling catheters	1.548 (1.259 -1.903)	<0.001		
Prior surgery	3.235 (1.233-8.486)	0.017		
Positive endotracheal tube culture of <i>S. maltophilia</i>	4.500 (1.714-11.816)	0.002		
Concomitant positive culture of <i>P. aeruginosa</i>	3.433 (1.333-8.844)	0.011		
Concomitant positive culture of MRSA	3.117 (1.217-7.984)	0.018		
Length of antibiotic use prior to positive culture	1.050 (1.015-1.087)	0.005		
Use of piperacillin/tazobactam	5.084 (1.449-17.832)	0.011		
Delayed treatment for <i>S. maltophilia</i> *	25.532 (5.679-114.793)	<0.001	18.684 (4.050- 86.188)	<0.001

CI: confidence interval; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; OR: odds ratio; RR: relative risk

*Variables found significant in the multivariate analysis

In this study, ICU admission and delayed effective treatment were identified as independent predictors of *S. maltophilia* mortality. Critically ill patients, with active *S. maltophilia* infection, who did not receive effective treatment within 48 hours were found to be more likely to die from infection after adjusted for other confounding variables, consistent with previous findings.¹³

Pulmonary disease has been found to be a significant risk factor for *S. maltophilia* mortality.² In this study, pulmonary disease [e.g. asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and acute respiratory distress syndrome] was the most frequent comorbidity and was marginally significant ($P=0.062$) in the univariate analysis. The respiratory tract was also the most common site of *S. maltophilia* isolation; 44 out of 61 (72.1%) of patients with underlying pulmonary diseases had *S. maltophilia* isolated from a respiratory source. Isolation of a “high-risk” pathogen (e.g. *S. maltophilia*) was reported to be the most important predictor of mortality in late-onset ventilator-associated pneumonia.¹⁴ Overall, mortality among patients with respiratory isolation of *S. maltophilia* ranged from 50% to 61%.^{1,15,16} These results suggest that although *S. maltophilia* has been considered as a low-virulent and opportunistic pathogen,² it may still be associated with a high mortality rate in patients with underlying pulmonary disease in intensive care units, even more so when *S. maltophilia* is isolated from a respiratory source. *S. maltophilia* infections in the ICU setting are directly related to increased patient morbidity and mortality depending, in part, on severity of illness upon admission.¹⁷

As with any retrospective study, there are several intrinsic limitations in our study. The primary attending physician might have dismissed the significance of positive culture of *S. maltophilia*. Effective antimicrobial treatment was either not instituted, or delayed until an infectious disease specialist was consulted. Hence, only 42 out of 60 patients with clinically active infection (as defined in this study) were treated. Among the 18 patients who did not receive treatment, 8 patients died of *S. maltophilia* infection and the remaining 10 patients died of other underlying (non-infectious) diseases. Furthermore, most positive cultures (76.7%) of *S. maltophilia* were polymicrobial in our study. This further reiterates the clinical dilemma and hence making it difficult to evaluate the independent contribution of *S. maltophilia* to the clinical symptoms in the infected patient. There is a paucity of clinical investigations on the optimal management for *S. maltophilia* infections. Current guidelines do not advocate treatment for every patient with a positive *S. maltophilia* culture. The inability/difficulty to distinguish between colonisation and infection have fostered the belief that *S. maltophilia* is of limited pathogenicity. However, as we have shown in this study, *S. maltophilia* should not be

routinely dismissed as a coloniser when it is part of a polymicrobial culture. It is imperative to identify patients at high risk for mortality early in the course of illness. Thus, the identification of various predictors of mortality in these patients serves as an important tool to guide clinicians towards the evaluation of risk-to-benefit ratio in initiating therapy for *S. maltophilia* infections. Trimethoprim-sulfamethoxazole is the antibiotic of choice for the treatment of *S. maltophilia* infections; all isolates in our series were susceptible to trimethoprim-sulfamethoxazole. Given the deleterious outcomes, it may seem reasonable to include trimethoprim-sulfamethoxazole as therapy in critically ill patients at high risk for mortality promptly once *S. maltophilia* is isolated in sputum (and/or sterile sites). In vitro data suggest that newer fluoroquinolones (levofloxacin), minocycline and doxycycline may also be useful; however, clinical experience with these agents is limited.^{2,18}

In summary, ICU admission and delayed effective treatment for *S. maltophilia* were identified as independent risk factors of infection-attributed mortality in patients with positive cultures of *S. maltophilia*. Future research efforts should aim at improving strategies for the prevention and prompt effective treatment of *S. maltophilia* infections to reduce hospital mortality associated with *S. maltophilia* infections.

Disclosure/Potential Conflict of Interest

No financial support and potential conflict of interest to disclose by any author relating to this study. VHT has received unrestricted research grants from AstraZeneca and Merck, and speaking honoraria from Elan Pharmaceuticals and Schering Plough.

REFERENCES

1. Lai CH, Chi CY, Chen HP, Chen TL, Lai CJ, Fung CP, et al. Clinical characteristics and prognostic factors of patients with *Stenotrophomonas maltophilia* bacteremia. *J Microbiol Immunol Infect* 2004;37:350-8.
2. Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. *Clin Microbiol Rev* 1998;11:57-80.
3. Senol E. *Stenotrophomonas maltophilia*: the significance and role as a nosocomial pathogen. *J Hosp Infect* 2004;57:1-7.
4. Nicodemo AC, Garcia Paez JJ. Antimicrobial therapy of *Stenotrophomonas maltophilia* infections. *Eur J Clin Microbiol Infect Dis* 2007;26:229-37.
5. Horan TC, Gaynes RP. Surveillance of nosocomial infections. In: Mayhall CG, editor. *Hospital Epidemiology and Infection Control*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004:1659-702.
6. Friedman ND, Korman TM, Fairley CK, Franklin JC, Spelman DW. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. *J Infect* 2002;45:47-53.
7. VanCouvenerberghe CJ, Farver TB, Cohen SH. Risk factors associated with isolation of *Stenotrophomonas (Xanthomonas)*

- maltophilia* in clinical specimens. Infect Control Hosp Epidemiol 1997;18:316-21.
8. Muder RR, Harris AP, Muller S, Edmond M, Chow JW, Papadakis K, et al. Bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia*: a prospective, multicenter study of 91 episodes. Clin Infect Dis 1996;22: 508-12.
9. Jang TN, Wang FD, Wang LS, Liu CY, Liu IM. *Xanthomonas maltophilia* bacteremia: an analysis of 32 cases. J Formos Med Assoc 1992;91: 1170-6.
10. Senol E, DesJardin J, Stark PC, Barefoot L, Snyderman DR. Attributable mortality of *Stenotrophomonas maltophilia* bacteremia. Clin Infect Dis 2002;34:1653-6.
11. Labarca JA, Leber AL, Kern VL, Territo MC, Brankovic LE, Bruckner DA, et al. Outbreak of *Stenotrophomonas maltophilia* bacteremia in allogeneic bone marrow transplant patients: role of severe neutropenia and mucositis. Clin Infect Dis 2000;30:195-7.
12. Rispal P, Maugein J, Lasseur C, Marit G, Denisi R, Pellegrin JL, et al. *Xanthomonas maltophilia* nosocomial infections. A new threat. Apropos of 30 cases (French). Rev Med Interne 1994;15:808-12.
13. Vartivarian SE, Anaissie EJ, Kiwan EN, Papadakis KA. The clinical spectrum of *Stenotrophomonas (xanthomonas) maltophilia* respiratory infection. Semin Respir Crit Care Med 2000;21:349-55.
14. Kollef MH, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 1995;108:1655-62.
15. Penzak SR, Abate BJ. *Stenotrophomonas (Xanthomonas) maltophilia*: a multidrug-resistant nosocomial pathogen. Pharmacotherapy 1997;17:293-301.
16. Elting LS, Bodey GP. Septicemia due to *Xanthomonas* species and non-aeruginosa *Pseudomonas* species: increasing incidence of catheter-related infections. Medicine (Baltimore) 1990;69:296-306.
17. Bjerke HS, Leyerle B, Shabot MM. Impact of ICU infections on outcome from surgical care. Am Surg 1991;57:798-802.
18. Cohn ML, Waites KB. Antimicrobial activities of gatifloxacin against nosocomial isolates of *Stenotrophomonas maltophilia* measured by MIC and time-kill studies. Antimicrob Agents Chemother 2001;45:2126-8.