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Significance of positive *Stenotrophomonas maltophilia* culture in acute respiratory tract infection

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ABSTRACT: ***Stenotrophomonas maltophilia*** **is a common coloniser of the respiratory tract of patients with chronic lung disease, and, in the absence of pneumonia or bacteraemia, is often ignored by physicians at the Royal Perth Hospital (Perth, Australia). Experience at the Royal Perth Hospital was reviewed to determine whether ignoring *S. maltophilia* in this setting has any apparent effect on clinical outcome.**

All patients who presented with an acute respiratory illness and yielded a positive culture for *S. maltophilia* between 1995 and 2002 were retrospectively reviewed. All subjects had to yield a positive respiratory isolate of *S. maltophilia* and undergo chest radiography within 24 h of the isolate being obtained.

Ninety-two episodes were identified in 89 individuals; 64 showed no evidence of consolidation. Of the study group, 51 (80.0%) received no anti-*S. maltophilia* antibiotic therapy and 21 (32.8%) had a nosocomially acquired isolate. The overall mortality rate was 20.3%. There was no impact of anti-*S. maltophilia* therapy on outcome. The only independent predictor of mortality was serum albumin level.

As there was no measurable impact of antibiotic therapy, in the absence of consolidation, a positive respiratory tract isolate of *Stenotrophomonas maltophilia* probably represents colonisation of a severely impaired host rather than invasive disease.

KEYWORDS: **Outcome, respiratory, *Stenotrophomonas maltophilia*, treatment**

Stenotrophomonas maltophilia is a Gram-negative nonfermentive bacillus. It has previously been designated as *Pseudomonas maltophilia* and *Xanthomonas maltophilia* [1]. Owing to a combination of high innate antibiotic resistance, including two chromosomal cephalosporinases, one of which hydrolyses carbapenems [2], and selective antibiotic pressure, *S. maltophilia* is emerging as an important nosocomial pathogen.

Mortality rates of 10–60% in patients with bacteraemia due to *S. maltophilia* have been reported [2–5], largely influenced by their occurrence in critically ill, heavily immunosuppressed patients. However, the attributable mortality due to *S. maltophilia* bacteraemia appears to be equivalent to that for other nosocomial bacteraemias after adjusting for underlying disease status [6].

Although the respiratory system is the most common site of isolation and infection with *S. maltophilia* [7], the significance of a positive respiratory tract isolate in the absence of bacteraemia is less clear as transient asymptomatic carriage is not common, especially in the nosocomial setting [8–10]. Making a distinction between *S. maltophilia* colonisation and infection is made even more difficult by the frequent isolation of other organisms from the same specimen [8].

Therefore, although there is good evidence that *S. maltophilia* causes significant mortality in patients with nosocomial pneumonia [8, 11], in other clinical settings, the significance of a positive respiratory isolate is much less clear.

At the Royal Perth Hospital (Perth, Australia), there was quite a range of opinions regarding the need to treat *S. maltophilia* when isolated from sputum in the absence of pneumonia. Therefore, all case records from the period of 1995–2002 were reviewed to determine whether the decision to treat *S. maltophilia* impacted on outcome, and whether clinical indications for treatment could be determined.

METHODS

Patient identification and selection

All patients yielding a respiratory tract isolate of *S. maltophilia* at the Royal Perth Hospital between

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1995 and 2002 were identified from the hospital microbiology database. In order to qualify for this analysis, patients had to be documented as having at least two of the following at the time of the sputum culture: 1) increased dyspnoea; 2) productive cough; 3) fever; and 4) deterioration in oxygenation. Patients had to be hospitalised or in the emergency department at the time the respiratory sample was obtained to be included in the study. Case records were then reviewed for the data points of interest. Patients with radiological evidence of pneumonia were excluded from analysis of impact on therapy. This study was approved by the Ethics Committee of the Royal Perth Hospital.

Definitions

An episode of *S. maltophilia* was defined as a positive sputum sample, endotracheal tube aspirate, bronchial wash or lavage culture. If no specific therapy for *S. maltophilia* was given, then subsequent isolates obtained during the same hospital admission were not defined as a separate episode.

Nosocomial infection was defined as a positive culture for *S. maltophilia* >72 h after admission to hospital, or a positive culture on admission if the patient had been discharged from hospital in the past 14 days.

With respect to outcome, mortality was defined as death occurring within 14 days of the initial positive culture of *S. maltophilia*.

Applied Physiology, Age, and Chronic Health Evaluation (APACHE) II scores [12] were calculated from the worst physiological values on the day that the respiratory isolate was obtained.

Statistics

Differences in continuous variables were assessed using an unpaired t-test after checking for normality of distribution. Differences in categorical variables were assessed with Fisher's exact test. A p-value of <0.05 was considered significant.

RESULTS

A total of 89 individuals were identified as yielding a positive respiratory tract culture for *S. maltophilia* on 92 separate occasions. The mean±SD age of the patients was 60.2±18.1 yrs (range 19–95 yrs). There were 35 (39.3%) female and 54 (60.7%) male patients. The clinical diagnoses at the time of sputum culture were acute tracheobronchitis in 30 (32%) patients, acute exacerbation of chronic obstructive pulmonary disease in 27 (29%), nosocomial pneumonia in 17 (18%), community-acquired pneumonia in 11 (12%) and infective exacerbation of bronchiectasis in seven (7.5%). Of the nosocomial pneumonias, 15 out of 17 were in patients requiring mechanical ventilation (*i.e.* with suspected ventilator-associated pneumonia).

In 48 (52.2%) episodes, *S. maltophilia* was not the only respiratory pathogen cultured from the positive sample, with three or more potential pathogens being identified on eight (8.7%) occasions. The most common copathogens isolated were *P. aeruginosa* (n=16), *Klebsiella pneumoniae* (n=5), *Enterobacter* spp. (n=6), *Staphylococcus aureus* (n=4), *Escherichia coli* (n=3) and *Acinetobacter* spp. (n=3). Copathogens were identified in 14 (36.8%) of the 38 nosocomially acquired episodes and 20 (37.0%) of the community-acquired episodes ($p>0.1$). Amongst survivors, an additional sputum sample was obtained 7–28 days after the initial culture in 36% of those who did not receive specific anti-*S. maltophilia* antibiotic therapy and 57% of those who did. There was no documented chronic carriage of *S. maltophilia* in the treated or untreated groups.

Table 1 shows a comparison of the episodes with and without radiological evidence of pneumonia. There were no significant differences between episodes with and without pneumonia for the variables shown in table 1. The most common antibiotics received in the 30 days prior to the first positive culture for *S. maltophilia* were third-generation cephalosporins (n=27), a carbapenem (n=10), a macrolide (n=7) and a β-lactam/β-lactamase inhibitor combination (n=6). All third-generation cephalosporins and carbapenems were received within the 10 days prior to the positive culture for *S. maltophilia*. Apart from the four patients who had a second identified episode, only one other patient had a previously documented infection with *S. maltophilia*. With respect to other prior culture of multidrug-resistant pathogens, eight patients had documentation of previous culture of *P. aeruginosa*, two of whom had documented bronchiectasis. No patient had cystic fibrosis. With respect to malignancies, 15 were solid-organ malignant tumours and eight haematological malignancies.

As the vast majority (82%) of patients with pneumonia received anti-*S. maltophilia* antibiotics and significant mortality has been attributed to pneumonia due to this organism [8, 11], further analysis was limited to the patients without radiological evidence of pneumonia. Table 2 shows a summary of the demographic information for both community-acquired and nosocomially acquired episodes after excluding the 28 (30.4%)

TABLE 1 Summary of cases by the presence or absence of radiological pneumonia

	Present	Absent	p-value
Subjects n	28	64	
Age yrs	56.9±17.7	62.4±17.7	NS
Females	10 (35.7)	25 (45.3)	NS
Deceased	8 (28.6)	13 (20.3)	NS
Nosocomially acquired	17 (60.7)	21 (32.8)	0.02
Mechanical ventilation	15 (53.6)	19 (29.7)	0.04
COPD	8 (28.6)	32 (50.0)	NS
Cardiac failure	6 (21.4)	17 (26.6)	NS
Malignancy	7 (25.0)	15 (23.4)	NS
Bronchiectasis	0 (0.0)	7 (10.9)	NS
Current smoker	4 (14.3)	16 (25.0)	NS
Ex-smoker	16 (57.1)	31 (48.4)	NS
Oral corticosteroids	16 (57.1)	35 (54.7)	NS
Antibiotics in past 30 days	21 (75.0)	45 (70.3)	NS
Antibiotics in past 90 days	25 (89.3)	59 (92.2)	NS
Polymicrobial infection	18 (64.3)	31 (48.4)	NS
APACHE II score	16.4±7.3	15.7±7.1	NS

Data are presented as mean±SD and n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; APACHE: Applied Physiology, Age, and Chronic Health Evaluation; NS: nonsignificant.

TABLE 2 Demographic information for community-acquired and nosocomially acquired *Stenotrophomonas maltophilia* isolates from patients without pneumonia

	Community	Nosocomial	p-value
Subjects n	43	21	
Age yrs	64.9±18.2	57.3±16.0	NS
Females	15 (34.9)	14 (66.7)	0.03
Deceased	5 (11.6)	8 (38.1)	0.02
Anti-*S. maltophilia* therapy	15 (34.9)	3 (14.3)	NS
Deceased	5 (11.6)	8 (38.1)	NS
Mechanical ventilation	4 (9.3)	17 (80.1)	<0.0001
COPD	24 (55.8)	7 (33.3)	NS
Cardiac failure	12 (27.9)	5 (23.8)	NS
Malignancy	10 (23.2)	5 (23.8)	NS
Bronchiectasis	7 (16.3)	0 (0.0)	NS
Current smoker	8 (18.6)	8 (38.1)	NS
Ex-smoker	25 (58.1)	6 (28.6)	NS
Oral corticosteroids	29 (67.4)	6 (28.6)	0.007
Antibiotics in past 30 days	24 (55.8)	21 (100)	0.0001
Antibiotics in past 90 days	38 (88.4)	21 (100)	NS
Polymicrobial infection	17 (39.5)	14 (66.7)	0.04

Data are presented as mean±SD and n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; NS: nonsignificant.

episodes with pneumonia. The only significant differences were the expected higher frequency of mechanical ventilation in patients with nosocomially acquired infection ($p<0.0001$), the greater frequency of antibiotic use in the past 30 days ($p=0.0001$), greater use of corticosteroids ($p=0.007$) and the greater frequency of polymicrobial infection ($p=0.04$) in the same group. Anti-*S. maltophilia* therapy was sulfamethoxazole/trimethoprim with (n=6) or without (n=12) ticarcillin/clavulanic acid.

Table 3 compares the fatal and nonfatal cases with respect to key comorbid and clinical features. Compared with survivors, nonsurvivors exhibited a substantially lower white cell count at the time of culture ($p=0.02$) and a substantially higher serum albumin concentration ($p<0.0001$), and were significantly more likely to have additional pathogens identified in the same respiratory sample ($p=0.005$). The difference in maximum recorded respiratory frequency also approached significance ($p=0.06$). As would be expected, the APACHE II score was also substantially lower in survivors ($p<0.0001$).

Logistic regression analysis incorporating all of the factors in table 3 (except composite APACHE II score) plus other chronic organ failures and significant interactions found that the only independent predictor of death was serum albumin concentration ($p=0.006$). Neither anti-*S. maltophilia* therapy ($p=0.485$) nor polymicrobial infection ($p=0.124$) was an independent predictor of outcome.

Analysis of patients who did and did not receive specific anti-*S. maltophilia* therapy was conducted at both a univariate (table 4) and multivariate level, incorporating all of the factors in tables 2 and 3. No comorbid or clinical feature, including

TABLE 3 Summary of fatal and nonfatal cases without pneumonia

	Fatal	Nonfatal	p-value
Subjects n	13	51	
Nosocomially acquired	8 (61.6)	13 (25.5)	0.02
Anti-*S. maltophilia* therapy	4 (30.8)	14 (27.5)	NS
Age yrs	59.2±16.6	63.1±18.1	NS
Females	6 (46.2)	23 (45.1)	NS
Mechanical ventilation	8 (61.6)	11 (21.6)	0.01
COPD	4 (30.8)	27 (52.9)	NS
Cardiac failure	1 (7.7)	16 (31.4)	NS
Malignancy	3 (23.1)	12 (23.5)	NS
Maximum f_C beats·min^{-1}	113.9±22.2	105.9±19.1	NS
Maximum f_R breaths·min^{-1}	27.4±7.4	24.2±4.6	NS
White cell count 10^9 cells·L^{-1}	14.9±7.1	10.2±5.9	0.02
Serum albumin g·L^{-1}	24.3±5.3	32.9±6.7	<0.0001
Polymicrobial infection	11 (84.6)	20 (39.2)	0.005
APACHE II score	19.3±9.4	10.4±5.9	<0.0001

Data are presented as mean±SD and n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; f_C: cardiac frequency; f_R: respiratory frequency; APACHE: Applied Physiology, Age, and Chronic Health Evaluation; NS: nonsignificant.

APACHE II score, was found that predicted selection of specific anti-*S. maltophilia* therapy. The apparent trend to lower white cell count in those treated was not significant ($p=0.09$).

The various subsets were also analysed for an influence of specific anti-*S. maltophilia* therapy on nonmortality outcomes. For community-acquired isolates, there was no significant

TABLE 4 Comparison of treated and untreated episodes

	Treated	Untreated	p-value
Subjects n	18	51	
Nosocomially acquired	2 (11.1)	19 (37.3)	NS
Females	6 (33.3)	23 (45.1)	NS
Age yrs	58.7±19.7	63.7±17.0	NS
COPD	9 (50.0)	22 (43.1)	NS
Mechanical ventilation	2 (11.1)	17 (33.3)	NS
Cardiac failure	3 (16.7)	14 (27.5)	NS
Malignancy	5 (27.8)	10 (19.6)	NS
Maximum f_C beats·min^{-1}	105.9±20.9	108.4±19.7	NS
Maximum f_R breaths·min^{-1}	22.6±3.7	25.8±5.8	NS
White cell count 10^9 cells·L^{-1}	8.8±6.4	12.0±6.2	NS
Serum albumin g·L^{-1}	30.8±6.9	31.2±7.5	NS
Polymicrobial infection	9 (50.0)	22 (43.1)	NS
APACHE II score	15.9±6.9	16.1±7.3	NS

Data are presented as mean±SD and n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; f_C: cardiac frequency; f_R: respiratory frequency; APACHE: Applied Physiology, Age, and Chronic Health Evaluation; NS: nonsignificant.

difference in the length of hospital stay in survivors who received specific anti-*S. maltophilia* therapy (mean±SD 20.2±14.5 days) compared with those who did not (16.4±15.4 days). Similarly, there was no difference in the proportion of patients readmitted with a respiratory tract infection in the 3 months after discharge from hospital (therapy group 27%; nontherapy group 26%).

DISCUSSION

Although nosocomial bacteraemia and ventilator-associated pneumonia due to *S. maltophilia* show significant mortality and morbidity [8, 11], it was not possible to attribute any excess mortality or morbidity in the absence of pneumonia. Although overall mortality rates were high, the absence of any apparent effect of treatment is more consistent with the acquisition of *S. maltophilia* being a marker of severe underlying life-limiting illnesses than of *S. maltophilia* being a highly virulent pathogen in this setting. Given the high frequency of multiple pathogens, in the absence of consolidation, isolation of *S. maltophilia* may not require antibiotic therapy as the majority of patients in this group do not appear to benefit from treatment.

The argument that most isolates of *S. maltophilia* from the respiratory tract represent colonisation rather than invasive disease is supported by several findings. First, and most importantly, specific anti-*S. maltophilia* antibiotic therapy did not alter the outcome in patients without pneumonia. Secondly, even without antibiotic therapy, the overwhelming majority of patients cleared *S. maltophilia* from their respiratory tract. Thirdly, in the majority of cases, *S. maltophilia* was not the only pathogen isolated. Finally, the only independent predictor of survival was serum albumin concentration. This strongly suggests that the isolation of *S. maltophilia* is an indication of a severely compromised host rather than *S. maltophilia* being an extremely virulent opportunistic pathogen.

Although treatment of *S. maltophilia* may not be critical, physicians still need to be cautious in their selection of antibiotic therapy when it is isolated. Given the extremely high frequency of multiple pathogens observed in the present study and in others [7, 8, 10], limiting antibiotic therapy to cover only *S. maltophilia* may be dangerous, as many of the typical copathogens are resistant to sulfamethoxazole/trimpethoprim. It should also be noted that both gatifloxacin and doxycycline appear to be good alternatives to sulfamethoxazole/trimethoprim *in vitro* [13], although efficacy in clinical trials has not been assessed.

Given the retrospective observational nature of the present study, there are clearly limitations to the interpretation of the data. In particular, the possibility that physicians selected patients for treatment based on an unidentifiable criterion cannot be excluded. However, the comparison shown in table 4 suggests that the treated and untreated groups were very similar. Furthermore, the finding that the only independent predictor of mortality was serum albumin concentration strengthens the argument that a respiratory isolate of *S. maltophilia* indicates a severely compromised host rather than invasive disease with a highly virulent pathogen.

In summary, in the absence of pneumonia-specific antibiotic therapy, *Stenotrophomonas maltophilia* isolated from the respiratory tract does not appear to affect outcome. When *Stenotrophomonas maltophilia* is isolated, physicians should be alert to the high probability of multiple pathogens being present. Although respiratory tract colonisation does not appear to have adverse implications, the isolation of *Stenotrophomonas maltophilia* indicates a severely compromised host with a high likelihood of mortality attributable to the underlying disease processes.

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