Original Article

Analysis of Stenotrophomonas maltophilia infections in lower respiratory tract samples at a university hospital: 5 year data

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ABSTRACT

Objectives

Patients with reported *Stenotrophomonas maltophilia* (*S. maltophilia*) growth in lower respiratory tract samples were investigated. The results of these patients were assessed by clinicians as either infection or colonization. The data of patients considered to have *S. maltophilia* infection were compared to those considered to have colonization to explore factors associated with infection.

Methods

Parameters including as age, length of hospital stay, duration of *S. maltophilia* growth after hospital admission, sex, unit, department, specimen type, mechanical ventilation treatment status, antimicrobial susceptibility results, comorbidities, survival, and antimicrobials used during the period from hospital admission to *S. maltophilia* growth were investigated. Additionally, some biochemical parameters that were examined include the day of hospital admission, the day of sample collection when the bacterium was isolated (±1 day), and the day of discharge/died.

Results

The infection group had a significantly higher rate of admissions to internal medical departments and more cases of discharge/died. The infection group showed a lower amount of aminoglycoside antibiotic usage and significantly higher levels of BUN, creatinine, neutrophils, and neutrophil-to-lymphocyte ratio on their day of discharge/died.

Conclusion

Being admitted to internal medical departments and receiving aminoglycoside treatment were identified to be factors associated with *S. maltophilia* infection. These patients should be monitored for infection markers such as CRP and neutrophil count, as well as renal function tests. It should be noted that being infected with *S. maltophilia* is an independent risk factor for mortality.

Keywords

Bacterial pneumonia; colonization, infection; *Stenotrophomonas maltophilia*

INTRODUCTION

Stenotrophomonas maltophilia (*S. maltophilia*) was initially isolated in 1943 and named *Bacterium bookeri.* After subsequent name changes as *Pseudomonas maltophilia* and *Xanthomonas maltophilia*, it acquired its current name in DNA-rRNA hybridization studies and by 16S rRNA sequencing. *S. maltophilia* is an obligate aerobic and motile bacterium with several polar flagella and is classified as a Gram-negative bacillus. It predominantly causes respiratory tract infections such as pneumonia and acute exacerbations of chronic obstructive pulmonary disease[1].

Gram-negative bacteria are the most common pathogens causing hospital-acquired pneumonia cases. While 55-85% of hospital-acquired pneumonias are attributed to Gram-negative bacteria, 20-30% are caused by Gram-positive bacteria, and 40-60% are polymicrobial in nature. Hospital-acquired pneumonia is the second most common healthcare-associated infection

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following urinary tract infections and is significantly associated with higher morbidity and mortality rates. It is defined as pneumonia that occurs 48 hours after hospital admission in a patient who did not have pneumonia at the time of their admission. The incidence of hospital-acquired pneumonia is 5-10 cases per 1000 hospital admissions and accounts for approximately 15% of healthcare-associated infections[2,3].

One-third of hospital-acquired pneumonia cases occur in intensive care units, with approximately 90% of these cases being associated with mechanical ventilation. Pneumonia occurring outside of the intensive care unit is more frequently observed in elderly patients, immunocompromised individuals, those who have undergone surgery, and those receiving enteral nutrition via a nasogastric tube. These cases prolong the average hospital stay by seven to nine days and have a crude mortality rate ranging from 30% to 70%, while most of these patients succumb to underlying diseases rather than the pneumonia itself. The attributable mortality rate of pneumonia is 33-50%[2].

In our study, we examined patients whose lower respiratory tract samples showed *S. maltophilia* growth reported by the Medical Microbiology Laboratory between 2015 and 2020. The results of these patients were assessed by clinicians as either infection or colonization. By comparing the data of patients considered to have *S. maltophilia* infection to those considered to have colonization, we investigated factors associated with infection.

MATERIALS AND METHODS

In our laboratory, Gram staining and culture are used for the evaluation of lower respiratory tract samples. A semi-quantitative method is employed for culture studies, and in cases where normal flora dominates in moderate to heavy growth, identification and antimicrobial susceptibility testing are performed. Samples with minimal growth or growth that does not dominate normal flora were excluded from this study. Conventional methods and the VITEK-2 automated system (bioMérieux, France) were used for identification, while Kirby-Bauer disk diffusion (Oxoid, United Kingdom) and the VITEK-2 automated system (bioMérieux, France) were used for antimicrobial susceptibility testing. The evaluation of antimicrobial susceptibility followed the guidelines provided by the Clinical and Laboratory Standards Institute in 2015 and the European Committee on Antimicrobial Susceptibility Testing between 2016 and 2020[4,5].

Lower respiratory tract samples sent to our laboratory from January 2015 to January 2020 were retrospectively reviewed over a five-year period. For this purpose, hospital information systems and patient records were examined. Only the first isolates collected from patients were included in the study. Parameters such as age, length of hospital stay, duration of *S. maltophilia* growth after hospital admission, sex, unit, department, specimen type, mechanical ventilation treatment status, antimicrobial susceptibility results, comorbidities, survival, and antimicrobials used during the period from hospital admission to *S. maltophilia* growth were investigated. Additionally, some biochemical parameters that examined included the day of hospital admission, the day of sample collection when the bacterium was isolated (±1 day), and the day of discharge/died. The decision regarding whether the isolated *S. maltophilia* was considered an infectious agent or a colonization case was made by the patient's attending physician during their hospitalization. Accordingly, the patients were divided into two groups: the infection group and the colonization group.

Statistical analyses were performed using the SPSS version 22 software (SPSS Inc., Chicago, IL, USA). Depending on the analysis, the Chi-squared test, Fisher's exact test, independent-samples t-test, and the Mann-Whitney U test were used to examine the relationships between different variables In the multivariate analyses, independent predictors of the infectious agent/colonization outcome were examined using logistic regression analysis, taking into account the potential factors identified in the univariate analyses. Model fit was assessed using the Hosmer-Lemeshow test. Cases with a Type 1 error rate below 5% were considered statistically significant.

ETHICAL APPROVAL

The permission to conduct the research was obtained from the Non-Interventional Ethics Committee of Trakya University (approval number: TÜTF-GOBAEK 2022/95). Before commencing the research, institutional permission was obtained from the faculty of medicine where the study was conducted.

RESULTS

Over the course of five years, *S. maltophilia* was isolated in the respiratory tract cultures of a total of 93 different patients in our laboratory. The infection group had a significantly higher rate of admissions to internal medical departments and more cases of discharge/died (Table 1).

The infection group showed a lower amount of aminoglycoside antibiotic usage and significantly higher levels of BUN, creatinine, neutrophils, and neutrophil-to-lymphocyte ratio on the day of discharge/died (Tables 2, 3). Additionally, in these patients, CRP levels were significantly higher both on the day of sample collection when the bacterium was isolated and on the day of their discharge/died (Table 2, 3).

The results of the logistic regression analysis revealed that being admitted to internal medical departments increased the risk of infection by a factor of 0.217 (Table 4).

DISCUSSION

There is no gold standard method for diagnosing hospital-acquired pneumonia cases. Diagnosis is based on clinical findings or microbiological testing in the presence of clinical suspicion[2]. To evaluate whether the microorganism isolated in culture is an indicator of colonization or an infectious agent, it is recommended to measure the unit count of colony-forming units per milliliter or rate bacterial growth as mild, moderate, or severe using a semi-quantitative approach[6]. However, in cases of moderate or severe growth or when the flora is dominant, the clinician can determine colonization based on the patient's clinical evaluation.

The SENTRY study, which followed pneumonia patients and examined data covering approximately twenty years, showed that the proportion of Gram-negative bacilli as the causative agent of pneumonia increased from 70.0-74.7% to 80.9-82.9% in the comparisons of data from 1997-98 to data from 2015-16[7]. *S. maltophilia* is the seventh most common pathogen in North America, with a detection rate increasing from 2.9% in 2003-2004 to 5.6% in 2013-2014. In Europe, it is the eighth most common pathogen, with a detection rate increasing from 2.7% in 1997-1998 to 4.4% in 2015-2016[7]. The Surveillance of Antimicrobial Use and Antimicrobial Resistance in German Intensive Care Units (SARI) identified *S. maltophilia* as one of the 13 most significant organisms associated with nosocomial infections[8].

S. maltophilia can be isolated together with other bacteria such as *Pseudomonas aeruginosa*, *Burkholderia spp., Staphylococcus aureus, Acinetobacter baumannii, Escherichia coli, Klebsiella spp., Enterobacter spp., Enterococcus spp., Bacteroides spp., Corynebacterium spp.*, and *Candida albicans* from patient samples[1,9]. Although mostly isolated as a single agent in this study, the most common bacterium simultaneously found with *S. maltophilia* was *Pseudomonas spp*.

Knowing the risk factors for *S. maltophilia* pneumonia and providing targeted empirical treatment early on are key to reducing mortality rates[9]. Factors related to host and treatment, such as the severity of the underlying illness, history of surgery, changes in consciousness, mechanical ventilation status, invasive interventions in the gastrointestinal system, antibiotic use, other medications, and the application of invasive respiratory devices and equipment, play an important role in the pathogenesis of hospital-acquired pneumonia[2]. A meta-analysis study showed associations between hospital-acquired pneumonia and underlying diseases (e.g., COPD and malignant tumors), mechanical ventilation, and the use of broad-spectrum antibiotics, while no associations were found between this form of pneumonia and immunodeficiency, diabetes mellitus, or renal failure[9]. Other studies identified factors such as carbapenem use, being in the intensive care unit, malignancy, presence of permanent devices, chronic respiratory diseases, immunocompromised host, prior antibiotic use, and prolonged hospitalization[1,8]. In our study, being admitted to internal medical departments and receiving aminoglycoside treatment before isolation were found to be significant predictors of infection. The natural resistance of *S. maltophilia* to aminoglycosides may suggest its selection over other bacteria. However, no association was found between infection and the use of carbapenem, to which the bacterium is also naturally resistant. Although antibiotic use has been found to be related to *S. maltophilia* infection in different studies, the specific antibiotic group varies. Some revealed an association between *S. maltophilia* infection and metronidazole, while others have found an association

of the former with carbapenems[10,11]. Therefore, the variability in results regarding antibiotic groups makes it challenging to reach a definitive conclusion. On the other hand, our study showed an association between infection cases and higher mortality rates. This suggested that *S. maltophilia* infection poses a serious risk for patient mortality and indicated that the diagnosis of infection by clinicians was accurate.

The SENTRY results from 2004 showed a resistance rate of 3.8% to TMP-SMX in *S. maltophilia*[12]. The SENTRY results from 1997 to 1999 showed resistance levels of up to 10% across Europe[13]. According to the CHINET bacterial resistance surveillance data, levofloxacin resistance in *S. maltophilia* is 10.8%, and SXT resistance is 6.7%[9]. In a study conducted on *S. maltophilia* strains isolated from pneumonia patients, levofloxacin resistance was found to be 20.4%, and SXT resistance was 5.8%[7]. In our study, levofloxacin resistance in the same factor was found to be 8.2%, and SXT resistance was 9.7%. These results indicated similar resistance rates to those reported in extensive studies worldwide[9,13].

In the comparisons of the biochemical data on the day of admission, the day of sample collection, and the day of discharge/died, it was observed that BUN, creatinine, neutrophils, and CRP were significantly higher in the infected patients, particularly on the day of their discharge/died. These values did not show significant differences on the day of admission. *S. maltophilia* is a nosocomial pathogen, and therefore, it is natural to find elevated levels of parameters indicating infection such as neutrophils and CRP. Many drugs used in hospitals have an effect on parameters such as BUN and creatinine. One of the groups of such drugs is antimicrobials. The prolonged or higher-dose use of antimicrobials in patients diagnosed with infection may affect their kidney function test results. In our study, aminoglycoside use prior to infection was found to be associated with higher levels of BUN and creatinine. Considering the nephrotoxic effect of aminoglycosides, it is possible that these agents contribute to impaired kidney function tests. Therefore, the association between elevated BUN and creatinine levels and infection in our study was consistent.

S. maltophilia is naturally resistant to benzylpenicillin, first- and second-generation cephalosporins, carbapenems, aminoglycosides, trimethoprim, and tetracycline[14]. Antimicrobials that are effective against this microorganism are typically not included in empirical antimicrobial regimens[15,16]. Despite being a significant clinical agent compared to other Gram-negative pathogens, *S. maltophilia* has been studied to a limited extent[15].

Our study had some limitations. It was conducted at a single center, which limits the generalizability of our findings. Additionally, deaths that could have been attributed to other causes should not be overlooked.

In conclusion, being admitted to internal medical departments and using aminoglycosides were identified as factors associated with *S. maltophilia* infection. Patients with *S. maltophilia* infection should have their CRP, neutrophil levels, and kidney function test results monitored. It should be noted that being infected with *S. maltophilia* is an independent risk factor for mortality.

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Conflict of interest

The authors have declared that there is no conflict of interest

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Table 1. Characteristics of the patients participating in the study

	Infection	Colonization	p
Age	64.00 (55.00-72.50)	64.00 (36.00-74.75)	0.442†
Length of hospital stay	26.50 (15.00-53.25)	35.00 (18.00-68.00)	0.479†
Duration of *S. maltophilia* growth after hospital admission	12.00 (6.00-27.75)	14.00 (5.00-30.50)	0.641†
Sex			
Female	15 (%28.3)	11 (%27.5)	0.932
Male	38 (%71.7)	29 (%72.5)	
Unit			
Intensive care	28 (%52.8)	18 (%45.0)	0.455
Ward	25 (%47.2)	22 (%55.0)	
Department			
Surgical medical	9 (%17)	12 (%30.0)	**0.034**
Internal medical	**39 (%73.6)**	19 (%47.5)	
Pediatric	5 (%9.4)	9 (%22.5)	
Specimen			
Sputum / BAL	41 (%77.4)	34 (%85.0)	0.356
Tracheal aspirate	12 (%22.6)	6 (%15.0)	
Mechanical ventilation			
Yes	32 (%60.4)	23 (%57.5)	0.780
No	21 (%39.6)	17 (%42.5)	
Levofloxacin			
Susceptible	45 (%91.8)	33 (%91.7)	1.000*
Resistant	4 (%8.2)	3 (%8.3)	
Trimethoprim sulfamethoxazole			
Susceptible	49 (%92.5)	35 (%87.5)	0.492*
Resistant	4 (%7.5)	5 (%12.5)	
Cancer			
Yes	22 (%41.5)	11 (%27.5)	0.162
No	31 (%58.5)	29 (%72.5)	
Diabetes mellitus			
Yes	6 (%11.3)	2 (%5)	0.459*
No	47 (%88.7)	38 (%95)	
Hypertension			
Yes	8 (%15.1)	5 (% 12.5)	0.721
No	45(%84.9)	35 (%87.5)	
Chronic obstructive pulmonary disease			
Yes	9 (%17)	10 (%25)	0.342
No	44 (%83)	30 (%75)	
Sepsis			
Yes	7 (%13.2)	2 (%5)	0.185
No	46 (%86.8)	38 (%95)	
Heart disease			
Yes	11 (%20.8)	9 (%22.5)	0.839
No	42 (%79.2)	31 (%77.5)	
Immunodeficiency			
Yes	15 (%28.3)	10 (%25.0)	0.722
No	38 (%71.7)	30 (%75.0)	
Pulmonary tuberculosis			
Yes	3 (%5.7)	1 (%2.5)	0.632*
No	50 (%94.3)	39 (%97.5)	
Chronic renal failure			
Yes	3 (%5.7)	2 (%5.0)	1.000
No	50 (%94.3)	38 (%95.0)	
Acute renal failure			
Yes	5 (%9.4)	2 (%5.0)	0.695
No	48 (%90.6)	38(%95.0)	
Radiotherapy			
Yes	8 (%15.1)	5 (%12.5)	0.721
No	45 (%84.9)	35 (%87.5)	
Chemotherapy			
Yes	7 (%13.2)	6 (%15.0)	0.805
No	46 (%86.8)	34 (%85.0)	
Survival			
Discharged	16(%30.2)	27(%67.5)	**0.000**
Died	37(%69.8)	13 (%32.5)	
*Fisher Exact †Mann Whitney U			

Table 2. Antimicrobials used during the period from hospital admission to *S. maltophilia* growth

	Infection	Colonization	p
Penicillin			
Yes	1 (%1.9)	0 (%0.0)	1.000*
No	52 (%98.1)	40 (%100)	
Beta lactam / beta lactamase inhibitor			
Yes	39 (%73.6)	23 (%57.5)	0.103
No	14 (%26.4)	17 (%42.5)	
Cephalosporin			
Yes	8 (%15.1)	7 (%17.5)	0.755
No	45 (%84.9)	33 (%82.5)	
Carbapenem			
Yes	25 (%47.2)	19 (%47.5)	0.975
No	28 (%52.8)	21 (%52.5)	
Aminoglycoside			
Yes	3 (%5.7)	10 (%25)	**0.008**
No	50 (%94.3)	30 (%75)	
Quinolone			
Yes	8 (%15.1)	7 (%17.5)	0.755
No	45 (%84.9)	33 (%82.5)	
Trimethoprim sulfamethoxazole			
Yes	4 (%7.5)	1 (%2.5)	0.281*
No	49 (%92.5)	39 (%97.5)	
Macrolide			
Yes	8 (%15.1)	7 (%17.5)	0.755
No	45 (%84.9)	33 (%82.5)	
Daptomycin			
Yes	1 (%1.9)	1 (%2.5)	0.678*
No	52 (%98.1)	39 (%97.5)	
Tigecycline			
Yes	4 (%7.5)	4 (%10)	0.722*
No	49 (%92.5)	36 (%90.0)	
Colistin			
Yes	9 (%17.0)	6 (%15.0)	0.797
No	44 (%83.0)	34 (%85.0)	
Linezolid			
Yes	7 (%13.2)	9 (%22.5)	0.240
No	46 (%86.8)	31 (%77.5)	
Glycopeptide			
Yes	9 (%17.0)	7 (%17.5)	0.948
No	44 (%83.0)	33 (%82.5)	
Metronidazole			
Yes	3 (%5.7)	2 (%5.0)	1.000
No	50 (%94.3)	38 (%95.0)	
Antifungal			
Yes	11 (%20.8)	9 (%22.5)	0.839
No	42 (%79.2)	31 (%77.5)	
Antiviral			
Yes	1 (%1.9)	1 (%2.5)	1.000*
No	52 (%98.1)	39 (%97.5)	
Antituberculosis			
Yes	2 (%3.8)	1 (%2.5)	1.000*
No	51 (%96.2)	39 (%97.5)	
*Fisher Exact			

Table 3. Biochemical parameters of patients

		Infection	Colonization	p
Alkaline phosphatase	Hospitalization	105.00 (77.00-209.00	85.50 (62.00-178.500)	0.183
	Bacterial growth	147.00 (85.00-217.00)	132.00 (75.00-281.00)	0.743
	Discharged / Died	144.50 (98.25-353.50)	183.50 (73.50-344.75)	0.804
Aspartate transaminase	Hospitalization	33.00 (23.25-61.25)	35.00 (24.00-67.50)	0.990
	Bacterial growth	39.50 (23.50-62.50)	29.00 (18.00-47.00)	0.132
	Discharged / Died	38.00 (22.50-82.25)	32.00 (26.50-50.50)	0.822
Alanine transaminase	Hospitalization	17.50 (11.00-39.75)	17.00 (9.50-31.50)	0.395
	Bacterial growth	25.50 (11.00-54.00)	23.50 (15.75-29.50)	0.563
	Discharged / Died	20.00 (14.00-40.00)	23.00 (13.75-39.75)	0.965
Blood urea nitrogen	Hospitalization	47.50 (28.25-75.00)	46.00 (34.00-72.50)	0.591
	Bacterial growth	52.50 (39.75-94.50)	57.00 (34.00-122.00)	0.900
	Discharged / Died	72.50 (38.25-113.75)	38.00 (27.00-82.00)	**0.028**
Creatinine	Hospitalization	0.90 (0.67-1.35)	0.90 (0.67-1.40)	0.809
	Bacterial growth	0.80 (0.52-1.10)	0.72 (0.55-1.23)	0.936
	Discharged / Died	0.90 (0.45-2.10)	0.61 (0.20-1.07)	**0.022**
Lymphocyte	Hospitalization	1.20 (0.63-2.10)	1.20 (0.60-2.50)	0.832
	Bacterial growth	0.82 (0.40-1.40)	1.24 (0.45-2.10)	0.212
	Discharged / Died	0.90 (0.60-1.34)	1.39 (0.68-2.20)	0.079
Neutrophil	Hospitalization	8.56 (4.94-12.91)	6.20 (4.09-10.98)	0.225
	Bacterial growth	8.5 (6.69-11.60)	6.70 (4.20-10.57)	0.066
	Discharged / Died	10.82 (5.96-17.25)	5.03 (3.05-10.08)	**0.019**
Erythrocyte sedimentation rate	Hospitalization	68.64±27.27	51.50±36.31	0.194*
	Bacterial growth	55.57±29.53	54.54±37.71	0.940*
	Discharged / Died	51.50±39.94	44.42±17.05	0.667*

		Infection	Colonization	p
Platelet	Hospitalization	238.00 (176.00-294.00)	229.00 (118.50-313.50)	0.674
	Bacterial growth	206.34±141.27	214.25±119.89	0.786*
	Discharged / Died	190.35±147.20	205.19±131.50	0.650*
Hemoglobin	Hospitalization	9.35 (8.80-11.17)	10.40 (8.40-11.90)	0.252*
	Bacterial growth	11.51±2.36	11.60±3.23	0.881*
	Discharged / Died	10.39±1.57	10.23±2.45	0.705
C-reactive protein	Hospitalization	8.22 (1.35-15.25)	5.64 (0.56-11.10)	0.186
	Bacterial growth	13.15 (5.21-20.75)	4.79 (0.97-15.47)	**0.004**
	Discharged / Died	14.60 (6.16-19.87)	2.59 (0.75-10.06)	**0.002**
Neutrophil / Lymphocyte	Hospitalization	6.18 (3.36-15.95)	6.20 (2.03-10.81)	0.545
	Bacterial growth	8.92 (4.33-16.53)	8.9 (4.36-16.50)	0.076
	Discharged / Died	9.98 (4.99-19.14)	4.55 (1.89-9.86)	**0.004**
Platelet / Lymphocyte	Hospitalization	195.31 (94.09-355.00)	143.75 (93.20-348.64)	0.426
	Bacterial growth	212.50 (122.52-359.13)	183.80 (97.80-305.38)	0.377
	Discharged / Died	195.65 (94.20-303.07)	116. 71 (75.05-234.64)	0.162
*Student t test				

Table 4. Logistic regression analysis results

Risk Factor	RR (95% CI)*	p
Department	0.217 (0.049-0.974)	**0.046**
Survival	0.355 (0.080-1.580)	0.174
Aminoglycoside	0	0.999
Creatinine (Discharged / Died)	0.985 (0.933-1.040)	0.589
C-reactive protein (Discharged / Died)	0.368 (0.904-1.038)	0.368
Neutrophil / Lymphocyte (Discharged / Died)	1.003 (0.963-1.044)	0.882

*RR: Estimated relative risk as indicated by odds ratio and 95% confidence interval

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