



Hospital-acquired *Stenotrophomonas maltophilia* Infections: Epidemiology and Risk Factors for Mortality

Nozokomiyal *Stenotrophomonas maltophilia* İnfeksiyonları: Epidemiyoloji ve Mortalite Risk Faktörlerinin Saptanması

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ABSTRACT

Introduction: Nosocomial *Stenotrophomonas maltophilia* infections have become a major concern in the recent years. In this study, we aimed to evaluate the clinical characteristics of nosocomial *S. maltophilia* infections and assess the risk factors for mortality.

Materials and Methods: An active and laboratory-based surveillance of hospital-acquired infections is conducted by the Infection Control Committee in high-risk and intensive care units of our hospital. In this study, these surveillance data were used to evaluate hospital-acquired *S. maltophilia* infections.

Results: In this study, 97 patients with hospital-acquired *S. maltophilia* infection were evaluated. Pneumonia (47.5%) and bacteremia (37.1%) were the most common types of infection. Hematologic malignancies, solid tumors, and chronic heart diseases were the most common underlying conditions. Central venous catheters, mechanic ventilation and immunosuppression were frequent risk factors in patients. Previous carbapenem use was common (78.4%). Seven-day and 28-day mortality were 25.7% and 46.3%, respectively. In the univariate analysis, hospital-acquired pneumonia was associated with seven-day mortality. Age, central line-associated bloodstream infections, ventilator-associated pneumonia, hospital-acquired pneumonia, mechanical ventilation and the presence of a urinary catheter were associated with 28-day mortality in univariate analysis. Age and hospital-acquired pneumonia were independently associated with 28-day mortality in the multivariate analysis. The treatment regimens did not have any impact on mortality. Tigecycline (5.6%), levofloxacin (7%), and trimethoprim-sulfamethoxazole (8.5%) exhibited the lowest resistance rates.

Conclusion: *S. maltophilia* is a nosocomial agent that mainly affects the critical and immunosuppressive patients. Pneumonia and bacteremia are the most common infection sites, leading to significant mortality. Age and presenting with hospital-acquired pneumonia are independent risk factors for mortality. Tigecycline has the lowest resistance rate among all antibiotics and it may be a good alternative for treatment. Although resistance to levofloxacin and trimethoprim-sulfamethoxazole is not high, it should be closely monitored.

Key Words: *Stenotrophomonas maltophilia*; Hospital-acquired; Nosocomial; Mortality; Risk factors

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ÖZ

Nozokomiyal *Stenotrophomonas maltophilia* İnfeksiyonları: Epidemiyoloji ve Mortalite Risk Faktörlerinin SaptanmasıDilek KARAMANLIOĞLU¹, Murat DİZBAY²¹ Etlik Şehir Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye² Gazi Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Ankara, Türkiye

Giriş: Nozokomiyal *Stenotrophomonas maltophilia* infeksiyonları son yıllarda önemli bir sorun haline gelmiştir. Bu çalışmada nozokomiyal *S. maltophilia* infeksiyonlarının klinik özelliklerinin ve mortalite için risk faktörlerinin değerlendirilmesi amaçlandı.

Materyal ve Metod: Hastanemizde yüksek riskli ve yoğun bakım ünitelerinde, İnfeksiyon Kontrol Komitesi tarafından hastane kaynaklı infeksiyonların aktif ve laboratuvar bazlı surveyanı yapılmaktadır. Bu çalışmada bu surveyanı verileri hastane kaynaklı *S. maltophilia* infeksiyonlarını değerlendirmek için kullanılmıştır.

Bulgular: Bu çalışmada hastane kökenli *S. maltophilia* infeksiyonu olan 97 hasta değerlendirildi. Pnömoni (%47.5) ve bakteremi (%37.1) en sık görülen infeksiyon türleriydi. Hematolojik malignite, solid tümör ve kronik kalp hastalığı en sık görülen altta yatan hastalıklardı. Santral venöz kateter, mekanik ventilasyon ve immünsupresyon, hastalarda sık görülen risk faktörleriydi. Daha önce karbapenem kullanımı yaygındı (%78.4). Yedi günlük ve 28 günlük mortalite sırasıyla %25.7 ve %46.3 idi. Tek değişkenli analizde hastane kökenli pnömoninin yedi günlük mortaliteyle ilişkili olduğu görüldü. Tek değişkenli analizde yaş, santral kateter ilişkili kan dolaşımı infeksiyonları, ventilatörle ilişkili pnömoni, hastane kaynaklı pnömoni, mekanik ventilasyon ve idrar sondası varlığı 28 günlük mortalite ile ilişkilendirildi. Çok değişkenli analizde yaş ve hastane kaynaklı pnömoni bağımsız olarak 28 günlük mortaliteyle ilişkilendirildi. Tedavi rejimlerinin mortalite üzerinde herhangi bir etkisi görülmedi. Tigesiklin (%5.6), levofloksasin (%7) ve trimetoprim-sülfametoksazol (%8.5) en düşük direnç oranlarına sahipti.

Sonuç: *S. maltophilia*, özellikle kritik ve immünsuprese hastaları etkileyen, nozokomiyal bir ajandır. Pnömoni ve bakteremi en sık görülen infeksiyon türüdür ve ciddi mortaliteye neden olmaktadır. Yaş ve hastane kaynaklı pnömoni mortalite için bağımsız risk faktörleridir. Tigesiklin tüm antibiyotikler arasında direnç oranı en düşük olanıdır ve tedavi için iyi bir alternatif olabilir. Levofloksasin ve trimetoprim-sülfametoksazole direnç yüksek olmasa da yakından izlenmelidir.

Anahtar Kelimeler: *Stenotrophomonas maltophilia*; Hastane kökenli; Nozokomiyal; Mortalite; Risk faktörleri

INTRODUCTION

Stenotrophomonas maltophilia is a non-fermentative gram-negative bacteria that has gained attention as a significant nosocomial pathogen in recent years. Infections caused by *S. maltophilia* are common among hospitalized patients with particular risk factors such as mechanical ventilation, central venous catheterization and immunosuppression. Long-term hospitalization and broad-spectrum antibiotic use also increase the risk of infection due to *S. maltophilia*^[1].

S. maltophilia can lead to various types of infections, including pneumonia, bloodstream infections, urinary tract infections, skin and soft tissue infections, abdominal infections, and central nervous system infections. Bacteremia and pneumonia are the most common nosocomial infection types, frequently causing complications and mortality^[2].

S. maltophilia is intrinsically resistant to many disinfectants and antibiotics such as beta-lactams, quinolones, aminoglycosides and tetracyclines. Therefore, treatment options are limited and clinical data on optimal treatment regimens is lacking^[3]. *S. maltophilia* infections are hard to manage in the clinical setting due to its intrinsic and acquired resistance mechanisms and high mortality rates.

In this study, we aimed to evaluate the clinical characteristics of nosocomial *S. maltophilia* infections and assess the risk factors for mortality.

MATERIALS and METHODS

This retrospective study was conducted at Gazi University Hospital, a 1007-bed teaching hospital, between January 2011 and June 2015. The study was approved by the Gazi University Ethics Committee with decision number 18 on October 12, 2015.

All adult and pediatric patients diagnosed with hospital-acquired *S. maltophilia* infection, of any type, during the study period were included in the study. The diagnosis of *S. maltophilia* infection was made by infection control nurses and doctors through active and laboratory-based surveillance. In our hospital, routine active surveillance of hospital-acquired infections includes high-risk units (hematology ward, bone marrow transplantation center, oncology and transplantation wards), and intensive care units (internal medicine, chest, anesthesia, cardiovascular surgery, neurology and pediatric intensive care units). Therefore, patients who were followed in these units were included in the study. Patients with hospital-acquired infections were visited daily by committee nurses and doctors. Targeted antimicrobial therapy was initiated for patients based on culture results, considering the in vitro antimicrobial susceptibility. A follow-up form, including the patients' clinical characteristics, was filled for each patient.

Hospital-acquired infections were diagnosed based on the "Centers for Diseases Control and Prevention" criteria^[4]. The data on demographics, comorbidities, risk factors, outcome, antibiotic therapies and antimicrobial susceptibility results were obtained from electronic and infection control committee records. The comorbidities of the patients included hematological malignancy, oncological malignancy, chronic heart disease (such as coronary artery disease/atherosclerotic heart disease or congestive heart failure), diabetes, chronic kidney disease, chronic lung disease (including chronic obstructive pulmonary disease, asthma, interstitial lung disease, cystic fibrosis), chronic liver disease, stem cell transplantation, and solid organ transplantation. The identified risk factors were central venous catheter use, immunosuppression, mechanical ventilation, urinary catheterization, neutropenia, steroid use, tracheostomy, and major surgical operations for infection. Factors associated with seven-day and 28-day mortalities were analyzed. Seven-day mortality was considered mortality attributable to the infection.

Microbiological Analysis

Automated microbiological systems (BD Phoenix) and conventional methods were used for bacterial identification. Antimicrobial susceptibility testing was performed manually using the Kirby-Bauer disk diffusion method and interpreted according to Clinical and Laboratory Standards Institute (CLSI) standards. Disk diffusion criteria determined by the Food and Drug Administration for *Enterobacteriaceae* were used for tigecycline susceptibility^[5]. The susceptibilities of cefoperazone-sulbactam, ciprofloxacin, and amikacin were interpreted according to the breakpoints determined for *Enterobacteriaceae* in the CLSI guidelines^[6].

Statistical Analysis

Statistical analyses were performed using the SPSS software version 15 (IBM Corp., Armonk, N.Y., USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether they are normally distributed. Categorical variables were expressed as numbers and percentages, while continuous variables were presented as median values with minimum and maximum ranges. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Non-parametric variables were analyzed with the Mann-Whitney U test, and parametric variables with the Student's t-test. Multivariate analysis was performed for the variables that were statistically significant in the univariate analysis. Values with a type-I error level of below 5% were considered statistically significant.

RESULTS

In this study, 97 patients with hospital-acquired *S. maltophilia* infection were evaluated. Sixty (61.9%) patients were male and the median age of all patients was 54 (min-max=3-101). Thirteen patients were 18 years old or younger, 53 were between the ages of 19 and 64, and 31 were 65 years old or older. A total of 47.4% of patients were in the ICU, while the others were in hematology, oncology, and transplantation units. Pneumonia was the most common infection type (47.5%).

Ventilator-associated pneumonia (VAP) was more frequent than hospital-acquired pneumonia (HAP) (28.9% and 18.6%, respectively). Bloodstream infections (37.1%) including central-line associated bloodstream infections (CLABSI, 20.6%) and laboratory-proven primary bloodstream infections (PBSI, 16.5%) constituted the second most frequent infection type.

The most common underlying diseases were hematological malignancy (48.4%), oncological malignancy (12.3%), and chronic heart disease (12.3%). When pediatric patients aged between three years and 18 years were evaluated, seven of these children had hematological malignancies, two had oncological malignancies, and four were being followed up in intensive care unit. These patients had similar risk factors as other patients in the study. Previous broad-spectrum antibiotic use was common. Seventy-eight point four percent of patients had used carbapenems, 25.8% had used third-generation cephalosporins, and 11.3% had used quinolones in the previous three months. The demographic data of the patients, infection types, risk factors for infection, and antimicrobials used for the treatment of *S. maltophilia* infections according to seven-day and 28-day mortality are presented in Table 1.

The seven-day and 28-day mortality rates were 25.7% and 46.3%, respectively. The 28-day mortality rates for patients with VAP, HAP, CLABSI, and PBSI were 64%, 72%, 20%, and 37.5%, respectively. In the univariate analysis, HAP was associated with seven-day mortality ($p < 0.001$). Age, CLABSI, VAP, HAP, mechanical ventilation and the presence of urinary catheter were associated with 28-day mortality in the univariate analysis (Table 1). Two factors were independently associated with 28-day mortality in the multivariate analysis: age ($p = 0.021$) and HAP ($p = 0.004$) (Table 2).

Antimicrobial susceptibility of *S. maltophilia* isolates is shown in Table 3. Tigecycline (94.3%), levofloxacin (93%), and trimethoprim-sulfamethoxazole (91.5%) were the most effective antibiotics according to the in vitro susceptibility results.

DISCUSSION

S. maltophilia is an important opportunistic pathogen that primarily affects hospitalized patients. Although it is known as a low-grade pathogen, it can cause serious infections in immunosuppressed patients^[7]. The most common infections caused by *S. maltophilia* are pneumonia and bloodstream infections. In the SENTRY study, a long-term surveillance study, it was reported that 56% of *S. maltophilia* infections were pneumonia and 34% were bloodstream infections^[8]. In our study, the most frequent infection type was pneumonia (47.5%) followed by bloodstream infection (37.1%), which is similar to the literature.

Known risk factors for *S. maltophilia* include intensive care unit admission, human immunodeficiency virus infection, cancer, cystic fibrosis, neutropenia, mechanical ventilation, central venous catheterization, previous surgery, trauma, and the use of broad-spectrum antibiotics^[9]. Hematologic cancers are also significant risk factors for *S. maltophilia* infections. In a study evaluating the *S. maltophilia* bacteremia, 68% of patients had malignancy, and half of them had acute leukemia^[10]. In our study, the presence of central venous catheterization (80%) was common in patients with *S. maltophilia* infection, followed by immunosuppression (63%), mechanical ventilation (50.5%) and neutropenia (40%). Forty-seven point four percent of patients were in the ICU and 48.5% had a hematologic malignancy as an underlying disease. It is well known that the use of broad-spectrum antibiotics, especially carbapenems, is a risk factor for *S. maltophilia* infection, and the rate of carbapenem use in our study was quite high (78.4%). In summary, the risk factors frequently mentioned in the literature were also common in our patient group.

S. maltophilia infections, particularly pneumonia and bloodstream infections, lead to significant mortality. Crude mortality rates have been reported between 25% and 51% in the literature^[11-13]. Mortality of patients with pneumonia was generally higher than that of those with bloodstream infections in many studies. Dizbay et al. reported a crude mortality rate of 71% in patients with *S. maltophilia* pneumonia and 50% in bloodstream infections^[2]. In our study, the seven-day mortality

Table 1. Clinical characteristics of patients with *S. maltophilia* infections according to seven-day and 28-day mortality

	Total n= 97 (%)	Seven-day Mortality		p	28-day Mortality		p
		Survived n= 72 (%)	Died n= 25 (%)		Survived (n= 52)	Died (n= 45)	
Age, median (min-max)	54 (3-101)	54 (3-95)	54 (20-101)	0.163	43 (3-87)	64 (18-101)	<0.001
Male sex	60 (61.9)	43 (59.7)	17 (68)	0.620	32 (61.5)	28 (62.2)	1.000
Time to infection, median (min-max)	25 (1-120)	23 (1-120)	30 (8-105)	0.364	23 (1-120)	30 (5-105)	0.085
Infection Type							
VAP	28 (28.9)	20 (2.7)	8 (32)	0.885	10 (19.2)	18 (40)	0.043
CLABSI	20 (20.6)	18 (25)	2 (8)	0.128	16 (30.7)	4 (8.8)	0.016
HAP	18 (18.6)	7 (9.7)	11 (44)	<0.001	5 (9.6)	13 (28.8)	0.030
PBSI	16 (16.5)	13 (18.1)	3 (12)	0.755	10 (19.2)	6 (13.3)	0.613
Urinary tract infection	9 (9.2)	8 (11.1)	1 (4)	0.439	7 (13.4)	2 (4.4)	0.170
Intraabdominal infection	2 (2.1)	2 (2.7)	0(0)	NA	2 (3.8)	0 (0)	NA
Skin-soft tissue infection	1 (1.0)	1 (1.3)	0(0)	NA	0 (0)	1 (2.2)	NA
Underlying Diseases							
Hematologic malignancy	47 (48.4)	36 (50)	11 (44)	0.776	27 (51.9)	20 (44.4)	0.595
Oncological malignancy	12 (12.3)	8 (11.1)	4 (16)	0.500	6 (11.5)	6 (13.3)	1.000
Chronic heart disease	12 (12.3)	7 (9.7)	5 (20)	0.287	5 (9.6)	7 (15.5)	0.564
Diabetes mellitus	11 (11.3)	9 (12.5)	2 (8)	0.723	5 (9.6)	6 (13.3)	0.799
Chronic renal disease	10 (10.3)	8 (11.1)	2 (8)	1.000	5 (9.6)	5 (11.1)	1.000
Chronic lung disease	10 (10.3)	6 (8.3)	4 (16)	0.276	5 (9.6)	5 (11.1)	1.000
Chronic liver disease	10 (10.3)	6 (8.3)	4 (16)	0.276	0 (0)	1 (2.2)	NA
Stem cell transplantation	5 (5.1)	4 (5.5)	1 (4)	1.000	4 (7.6)	1 (2.2)	0.369
Solid organ transplantation	2 (2.1)	2 (2.7)	0(0)	1.000	2 (3.8)	0 (0)	0.497
Risk Factors							
Central venous catheter	69 (71.1)	50 (69.4)	19 (76)	0.551	42 (80.7)	37 (82.2)	1.000
Immunosuppression	63 (64.9)	47 (65.2)	16 (64)	1.000	35 (67.3)	28 (62.2)	0.756
Mechanical ventilation	49 (50.5)	35 (48.6)	14 (56)	0.686	19 (36.5)	30 (66.6)	0.006
Urinary catheter	40 (41.2)	27 (37.5)	13 (52)	0.302	15 (28.8)	25 (55.5)	0.014
Neutropenia	39 (40.2)	27 (29.1)	12 (48)	0.493	20 (38.4)	19 (42.2)	0.866
Steroid use	30 (30.9)	21 (29.1)	9 (36)	0.700	14 (26.9)	16 (35.5)	0.486
Tracheostomy	11 (11.3)	10 (1.3)	1 (4)	0.279	5 (9.6)	6 (13.3)	0.799
Major surgery	8 (8.2)	6 (8.3)	2 (8)	1.000	4 (7.6)	4 (8.8)	1.000
Antimicrobial Therapy							
Trimethoprim sulfamethoxazole	36 (37.1)	28 (38.8)	8 (32)	0.708	17 (32.6)	19 (42.2)	0.448
Levofloxacin	28 (28.8)	24 (33.3)	4 (16)	0.164	14 (26.9)	14 (31.1)	0.819
Cefoperazone/sulbactam	11 (11.3)	7 (9.7)	4 (16)	0.467	4 (7.6)	7 (15.5)	0.370
Ciprofloxacin	9 (9.2)	8 (11.1)	1 (4)	0.439	6 (11.5)	3 (6.6)	0.498

VAP: Ventilator-associated pneumonia, CLABSI: Central line-associated bloodstream infection, HAP: Hospital-acquired pneumonia, PBSI: Bloodstream infection.

Table 2. Multivariate analysis of factors related to 28-day mortality of *S. maltophilia* infections

Factor	B	SE	Wald	df	OR (95% CI)	p
Age	0.027	0.012	5.292	1	1.027 (1.004-1.051)	0.021
CLABSI	-0.215	0.804	0.071	1	0.807 (0.167-3.903)	0.789
VAP	0.282	0.676	0.173	1	1.325 (0.352-4.987)	0.677
HAP	2.320	0.795	8.524	1	10.174 (2.144-48.293)	0.004
Mechanical ventilation	1.463	0.841	3.026	1	4.319 (0.831-22.451)	0.082
Urinary catheter	0.127	0.660	0.037	1	1.135 (0.311-4.141)	0.848

CLABSI: Central line-associated bloodstream infection, VAP: Ventilator-associated pneumonia, HAP: Hospital-acquired pneumonia, B: Regression coefficient, SE: Standard error, OR: Odds ratio, CI: Confidence interval, df: Degree of freedom.

Table 3. Antimicrobial susceptibility of *S. maltophilia* isolates

Antimicrobial	Number of Isolates	%
Tigecycline	50/53	94.4
Levofloxacin	80/86	93
Trimethoprim-sulfamethoxazole	86/94	91.5
Ciprofloxacin	44/51	86.3
Cefoperazone/sulbactam	28/45	62.2
Amikacin	34/61	55.7
Ceftazidime	37/68	54.4
Ticarcillin-clavulanic acid	3/16	18.7

rate, which we considered to reflect infection-related mortality, was 38%, and the 28-day mortality rate was 46.3%. The 28-day mortality of patients with pneumonia (VAP+HAP) was higher than that of patients with bloodstream infections (CLABSI+PBSI) (67.3% vs. 27.7%, respectively), similar to the literature. It is not unexpected that the mortality rates in our study were high, as our patient population consisted predominantly of critically ill and immunosuppressed patients.

There are several risk factors associated with mortality in patients with *S. maltophilia* infections. Admission to intensive care unit, advanced age, presence of CVC, chronic heart disease, hospitalization exceeding 30 days, previous use of broad-spectrum antibiotics, the need for vasopressors, autoimmune disease, and thrombocytopenia are the risk factors mentioned in the literature^[14-17]. In our study, age, CLABSI, VAP, HAP, mechanical ventilation and the presence of urinary catheter were associated with 28-day mortality in univariate analysis, however, only advanced age and HAP were still

statistically significant after multivariate analysis. Each one-year increase in age increased mortality by 1.027 times, and presenting with HAP increased mortality by 10 times, according to multivariate analysis. The only factor related to seven-day mortality in our study was presenting with HAP. Therefore, rapid access to culture results and early initiation of antibiotic treatment are crucial in patients with HAP.

Trimethoprim-sulfamethoxazole was the most commonly used antibiotic for the treatment of *S. maltophilia* infections in our study. Other antibiotics used included levofloxacin, cefoperazone-sulbactam, and ciprofloxacin. Interestingly, the treatment regimens did not have any impact on mortality. Many studies in the literature support our finding. A meta-analysis evaluating the clinical efficacy of fluoroquinolones and trimethoprim-sulfamethoxazole demonstrated comparable effects on mortality^[18].

Intrinsic resistance among *S. maltophilia* isolates limits antibiotic options and leads to difficulties in patient management. Additionally, the rising

antimicrobial resistance to first-line antibiotic options, such as trimethoprim-sulfamethoxazole and levofloxacin, is concerning. Recent data reveal that antimicrobial resistance to these agents has increased to 10-25%^[19-21]. Multidrug resistance is another concern. In a 10-year retrospective study, 16% of *S. maltophilia* isolates were resistant to trimethoprim-sulfamethoxazole and 32.7% of these resistant strains were also resistant to levofloxacin and colistin^[22]. In our study, resistance to trimethoprim-sulfamethoxazole and levofloxacin was below %10 (8.5% and 7%, respectively). Resistance rates were very high for ticarcillin-clavulanic acid, ceftazidime, amikacin and cefoperazone-sulbactam. Tigecycline had the lowest resistance rate among all tested antibiotics and may be a good alternative for treatment.

The main limitations of our study are its retrospective nature and the relatively small sample size. Additionally, the inclusion of pediatric patients in the study population may limit interpretation of the results.

CONCLUSION

In conclusion, *S. maltophilia* is an emerging nosocomial agent that primarily affects the critically ill and immunosuppressed patients. Pneumonia and bacteremia are the most common infection sites, leading to significant mortality. Age and presenting with hospital-acquired pneumonia are independent risk factors for mortality. The treatment regimens do not impact mortality. Tigecycline has the lowest resistance rate among all antibiotics and may be a good alternative for treatment. Although resistance to levofloxacin and trimethoprim-sulfamethoxazole is not high, it should be closely monitored.

ETHICS COMMITTEE APPROVAL

This study was approved by the Gazi University Clinical Research Ethics Committee (Decision no: 18, Date: 12.10.2015).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: MD, DK

Analysis/Interpretation: DK, MK

Data Collection or Processing: DK

Writing: DK

Review and Correction: MD, DK

Final Approval: MD

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