ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Children with *Stenotrophomonas maltophilia* Bacteremia

Stenotrophomonas maltophilia Bakteriyemili Çocuk Olguların Değerlendirilmesi

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Abstract

Introduction: *Stenotrophomonas maltophilia* (*S. maltophilia*) is a resistant gram-negative rod that can often cause serious infections, especially in patients with long hospital stays and using broad-spectrum antibiotics. In this study, clinical data, and mortality-related risk factors of patients with *S. maltophilia* bacteremia were evaluated.

Materials and Methods: Patients with *S. maltophilia* bacteremia included in this study and evaluated retrospectively, when hospitalized between 2013 and 2018 in our pediatric wards and intensive care units.

Results: A total of 67 patients had 100 *S. maltophilia* bacteremia in 70 different episodes. Sixty percent (n=40) of the cases were male and their median age were 9 months. Sixty-nine percent (n=46) of the cases were admitted in intensive care units. The most common comorbidity was malignancy. All bacteremias were healthcare associated, and 55% (n=55) were catheter-related. In the total of 70 episodes; 57% (n=37) of the patients had central venous catheters, 47% (n=33) were entubated. Fourty-seven percent (n=33) of the patients had broad spectrum antibiotic use over 14 days. In the blood cultures, 98% of *S. maltophilia*-producing strains were sensitive to trimethoprim-sulfamethoxazole. Ciprofloxacin and trimethoprim-sulfamethoxazole combination therapy had used for treatment. The mortality rate in the first 30 days was 16% (n=11). Mechanical ventilation was found to be significant ($p<0.05$) as a predisposing factor related to mortality.

Conclusion: *Stenotrophomonas maltophilia* is the causative pathogen in healthcare associated bloodstream infections especially in intensive care unit. In our study, 69% of the cases were admitted in the intensive care unit and mechanical ventilation status increased mortality.

Öz

Giriş: *Stenotrophomonas maltophilia* (*S. maltophilia*), uzun süre hastane yatışı olan ve geniş spektrumlu antibiyotik kullanan hastalarda ciddi enfeksiyonlara neden olabilen dirençli bir gram negatif basildir. Bu çalışmada *S. maltophilia* bakteriyemili hastaların klinik verileri ve mortalite ile ilişkili risk faktörleri değerlendirildi.

Gereç ve Yöntem: Çalışmada 2013-2018 yılları arasında pediatri servisleri ve yoğun bakım ünitelerinde yatırılan *S. maltophilia* bakteriyemili çocuk olgular retrospektif olarak değerlendirildi.

Bulgular: Toplam 67 hastada 70 farklı epizodda 100 kan kültüründe *S. maltophilia* üredi. Olguların %60'ı (n=40) erkekti ve ortanca yaşları 9 ay idi. Olguların %69'u (n=46) yoğun bakım ünitelerine yatırıldı. En sık eşlik eden hastalık malignite idi. Tüm bakteriyemiler sağlık hizmetiyle ilişkiliydi ve %55'i (n=55) kateterle ilişkili kan akımı enfeksiyonuydu. Toplam 70 epizodda; hastaların %57'sinde (n=37) santral venöz kateter vardı, %47'si (n=33) entübe idi. Hastaların %47'si (n=33) 14 gün üzerinde geniş spektrumlu antibiyotik kullandı. Kan kültürlerinde üreyen *S. maltophilia* suşlarının %98'i trimetoprim-sülfametoksazole duyarlıydı. Tedavide siprofloksasin ve trimethoprim-sülfametoksazol kombinasyon tedavisi kullanıldı. İlk 30 gün mortalite oranı %16 (n=11) idi. Mekanik ventilasyon mortalite ile ilişkili predispozan faktör olarak anlamlı (p<0,05) bulundu.
Sonuç: *Stenotrophomonas maltophilia*, özellikle yoğun bakımda sağlık hizmeti ilişkili kan dolaşımı enfeksiyonlarında önemli bir etken patojendir. Çalışmamızda olguların %69'u yoğun bakım ünitesine yatırılmış ve mekanik ventilasyon durumunun mortaliteyi artırdığı gösterilmiştir.

Introduction

Stenotrophomonas maltophilia is an opportunistic pathogen, which was previously called *Pseudomonas maltophilia* and later called *Xanthomonas maltophilia*. *Stenotrophomonas maltophilia* is an aerobe, non-fermentative gram-negative bacillus, particularly seen in patients receiving broad spectrum antibiotics such as carbapenem for a long time, and often cause respiratory tract infections, bacteremia, endocarditis, central nervous system and urinary tract infections. It can be isolated from soil, water, animals and hospital equipment. *Stenotrophomonas maltophilia* is capable of adhesion and biofilm formation of foreign substances and therefore can lead to catheter-related bloodstream infections and urinary tract infections.

The reported incidence of *S. maltophilia* infections ranged from 7.1 to 37.7 cases in 10,000 inpatients (1). *Stenotrophomonas maltophilia* has intrinsic resistance to aminoglycosides and beta-lactams including carbapenem (2,3). Although increasing resistance to quinolones had been reported, strains are usually susceptible to trimethoprim-sulfamethoxazole (4).

Risk factors associated with *S. maltophilia* infections include hospitalization in the intensive care unit (ICU), HIV infection, malignancy, cystic fibrosis, neutropenia, mechanical ventilation, central venous catheters indwelling, surgery, trauma and broad-spectrum antibiotics (1,5).

The aim of this study was to evaluate the clinical data of patients with *Stenotrophomonas maltophilia* bacteremia and to determine the risk factors.

Materials and Methods

Sixty-seven patients aged between 0-18 years were included in this study, who were detected *S. maltophilia* in their blood cultures (catheter and peripheral) and hospitalized between January 1, 2013 and January 31, 2018 in our pediatrics wards and intensive care units. Clinical conditions (duration and cause of hospitalization, comorbid disease, diagnosis at admission) and demographic characteristics of these cases, laboratory data (microbiological data), infection risk factors such as central venous catheter indwelling, urinary catheterization, mechanical ventilation, nasogastric tube, total parenteral nutrition, longterm use (>14 days) of broad-spectrum antibiotics, neutropenia status, received immunosuppressant therapy, prolonged hospitalization (≥14 days), *S. maltophilia* related infection rates, mortality rates were evaluated. The clinical and laboratory data of the patients were taken from our hospital electronic database. The use of third-generation cephalosporin, carbapenem, aminoglycoside and glycopeptide were accepted as the use of broad-spectrum antibiotics.

Ethics committee approval was obtained from the Clinical Research Ethics Committee of Uludağ University on July 10, 2018 with the decision numbered 2018-13/20. Participation involved informed consents.

Bacterial identification and antibiotic susceptibility tests are performed in BD Phoenix 100 (Becton Dickinson, USA) system in the bacteriology laboratory of our hospital. Antibiotic susceptibility tests are performed according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations. The best documented clinical response in this system is trimethoprim-sulfamethoxazole, and only the results of this antimicrobial susceptibility are indicated. It is considered as susceptible if the minimal inhibitory concentration of isolate to trimethoprim-sulfamethoxazole ≤4 mg/L, and >4 mg/L concentration is resistant (6,7).

Centers for Disease Control and Prevention (CDC, USA) criteria were used in the definitions (8-10).

Nosocomial infection defined as healthcare-associated infection. An infection is considered a healthcare-associated infection (HA) if the date of event of the National Healthcare Safety Network site-specific infection criterion occurs on or after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1. Primary bloodstream infection (BSI) is a laboratory confirmed bloodstream infection that is not secondary to an infection at another body site. Catheher related bloodstream infection is a laboratory confirmed bloodstream infection where an eligible BSI organism is identified and an eligible central line is present on the laboratory confirmed bloodstream infection date of event or the day before (8-10).

Polymicrobial infection defined as combination of two or more microorganisms together cause disease. The presence of one microorganism generates a niche for other pathogenic microorganisms to colonise, one microorganism predisposes the host to colonisation by other microorganisms (11). In this study, isolation of more than one microorganism from the same blood sample in a bacteremia episode was called polymicrobial bacteremia.

Isolation of the same organism from a patient, from the same source, was accepted as a single episode. In this study, when *S. maltophilia* was growth more than once in one patient in a single episode, only one was evaluated. Contamination was defined as the detection of contaminated bacteria in blood culture and also when the patient was lack of clinical significance and determination of negative acute phase reactants. Neutropenia was defined as the absolute neutrophil count <1500/mm^3.

All causes of death were detected within 30 days of the first positive blood culture.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 software (SPSS Inc.; Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). The results were expressed as frequency (percentage) and mean ± standard deviation or median (minimum-maximum and interquartile range). The chi-square or Fisher's Exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. In statistical analyzes, the significance level was determined as $p<0.05$.

Results

Stenotrophomonas maltophilia was detected in a total of 158 samples (blood, urine, tracheal aspirate fluid and other non-sterile body fluids) in the 5-year period between January 1, 2013 and January 31, 2018 in the pediatric wards and intensive care units in our hospital. In 67 patients with 70 different episodes, *S. maltophilia* detected in 100 (63%) blood culture. In 18 patients, more than one growth detection was found, and the mean number of growths were 2.5±1.1. Sixty percent (n=40) of the cases were male and the median ages were 9 months (mean 45±67, range 0-216 months). Sixty-nine percent (n=46) of the patients were hospitalized in the pediatric and neonatal intensive care unit. *Stenotrophomonas maltophilia* grew in the blood in patients median 14 (mean 28±35, range 1-150) days after hospitalization. There was no growth in a different site (endotracheal aspirate and/or body fluid) in the same episode. The underlying diseases were malignancy (20%), prematurity (18%) and neurological diseases (18%). There were no patients with cystic fibrosis. Patients were admitted to hospital mostly due to sepsis (50%) (Table 1).

Sixteen percent (n=16) of the blood cultures were from the catheter and 84% (n=84) were from the peripheral blood cultures. Fourteen percent (n=14) were considered as contamination. *Stenotrophomonas maltophilia* bacteremia episodes were all healthcare-associated and 55% (n=55) of them were catheter related. Twenty-six percent of all growth detection were polymicrobial and the most common accompanying microorganism was *Ralstonia pickettii*, followed by *Burkholderia cepaciae*.

Sixty-nine percent (n=46) of the 67 cases with *Stenotrophomonas maltophilia* bacteremias were inpatient in intensive care units, of which 78% (n=31) were associated with outbreak.

Sixty-nine percent (n=11/16) of the *S. maltophilia* bacteremias in the neonatal intensive care unit (n=16) were associated with outbreak. In this outbreak in February-April 2014, 20% (11/54) of the neonatal intensive care unit patients were affected and mortality was 45% (5/11). *Stenotrophomonas maltophilia*

isolates were not detected in the hospital equipment screening.

In the pediatric intensive care unit (n=30 patients), 67% (n=20) patients with *S. maltophilia* bacteremia were associated with the outbreak during 2013-2018 period. *Stenotrophomonas maltophilia* was detected in heparin vial in the period of October-December 2015.

Of the 70 episodes, 57% (n=37) had central venous catheter, 50% (n=35) had nasogastric catheter, 30% (n=21) had total parenteral nutrition, 10% (n=7) had urinary catheter, 47% (n=33) patient were intubated and 21% (n=15) were neutropenic. Fourty-seven percent (n=33) of the patients had more than 14 days of broad-spectrum antibiotic use and 20% (n=14) had immunosuppressive treatment (Table 2).

Ninety-eight percent (n=98) of the *S. maltophilia* bacteremia strains were susceptible to trimethoprim-sulfamethoxazole (TMP-SMX). Ciprofloxasin and trimethoprim-sulfamethoxazole combination therapy was used in the treatment. Control blood cultures became negative within 5 days.

Sixteen percent (n=11) of the patients died in the first 30 days. In two patients who had polymicrobial growth and died within first 30 days of growth detection; had concomitant microorganisms which were *B. cepaciae/ Ralstonia spp* in one case and *Staphylococcus aureus*

Table 1. Demographic characteristics of patients with *Stenotrophomonas maltophilia* bacteremia

	Mean ± SD (min-max, med)	n (%)
Total number of patients	-	67 (100)
Total episode	-	70 (100)
Age (month)	45±67 (0-216, 9)	-
Sex (boy)	-	40 (60)
ICU number of inpatients[a]	-	46 (69)
Duration of hospitalization (days)	28±35 (0-150, 14)	-
Major comorbidity (in 67 cases)		
Malignancy[b], n (%)	-	14 (20)
Prematurity, n (%)	-	12 (18)
Neurological[c], n (%)	-	12 (18)
CHD, n (%)	-	9 (13)
Metabolic disease, n (%)	-	8 (12)
Non-comorbid, n (%)	-	6 (9)
Postoperative inpatients[d], n (%)	-	3 (5)
Other (asthma, DM, immunodifeciency), n (%)	-	3 (5)
Diagnosis at admission (70 episodes)		
Sepsis, n (%)	-	35 (50)
Respiratory failure, n (%)	-	18 (26)
Heart failure, n (%)	-	5 (7)
Prematurity, n (%)	-	4 (6)
Liver failure, n (%)	-	3 (4)
Convulsion, n (%)	-	3 (4)
Renal failure, n (%)	-	1 (1.5)
Diabetic ketoacidosis, n (%)	-	1 (1.5)
Mortality in the first 30 days, n (%)	-	11 (16)

[a]Includes the total number of patients in pediatric intensive care unit and neonatal intensive care unit
[b]Includes malignancies, which most of them are hematologic and then oncologic malignancies
[c]Neurological comorbidities includes, cerebral palsy mostly and then epilepsy, spinomuscular atrophy
[d]It contains congenital diaphragmatic hernia and esophageal atresia
Mean: Average, SD: Standard deviation, min: Minimum, max: Maximum, med: Median, ICU: Internal care unit, CHD: Congenital heart disease, DM: Diyabetes mellitus

Table 2. Risk factors in *Stenotrophomonas maltophilia* bacteremia patients (70 episode)	
	n (%)
Use of broad-spectrum antibiotics	60 (90)
Central venous catheter	37 (57)
Nazogastric tube	35 (50)
Use of broad-spectrum antibiotics >14 days	33 (47)
Mechanical ventilation status	33 (47)
Prolonged admission (>14 days)*	29 (43)
Total parenteral nutrition	21 (30)
Neutropenia	15 (21)
Immunosuppressive therapy	14 (20)
Urinary catheterization	7 (10)

*The day of hospitalization at the time of growth detection was taken into consideration

in the other case. Polymicrobial growth was not detected as a mortality risk factor. When the mortality-related risk factors of *S. maltophilia* bacteremia were compared (Table 3), mechanical ventilation was found to increase mortality ($p<0.05$).

In 2013-2018 study period, in our clinic wards (included intensive care units, hematology and oncology clinics, pediatric infectious disease clinic wards and other pediatric clinic wards where the *S. maltophilia* bacteremia inpatients stayed) *S. maltophilia* infection rate was 0.86% (n=67/7764).

Stenotrophomonas maltophilia is one of the organisms isolated from the respiratory tract of patients with cystic fibrosis (CF). It simply colonizes the CF lung, and generally does not contribute to CF lung disease. In this study, there were no patients with cystic fibrosis.

Discussion

Stenotophomonas maltophilia is a gram-negative bacteria with low virulence and is an opportunistic multidrug-resistant pathogen that is usually detected in hospital, particularly in immunocompromised hosts. Risk factors associated with various *S. maltophilia* infection include underlying malignancy, cystic fibrosis, immunosuppressive therapy, the presence of a permanent central venous catheter, and exposure to broad-spectrum antibiotics (4). In this study, malignancy followed by prematurity and neurological diseases were the most common underlying disease in patients with *S. maltophilia* bacteremia. It has been observed as risk factors that broad-spectrum antibiotic use and invazive procedures such as central venous catheterization, nasogastric tube and mechanical ventilation were frequently used.

Most infections caused by *Stenotrophomonas maltophilia* require serious morbidity and long-term intensive care, with a mortality of 13-62% (12-14). In our study, 40% (n=27) of the patients died and the first 30 days mortality attributed to *S. maltophilia* was 16% (n=11). In a pediatric study which was designed by Tokatly Latzer et al. (5), *S. maltophilia* atrributed mortality was %16 which is similar to this study. In an adult study designed by Jeon et al. (15), the first 28 days mortality associated with *S. maltophilia* was found as 36.6% and the most important risk factors affecting the mortality were determined as hematological malignancy, SOFA (Sepsis-related Organ Failure Assessment) score and higher central venous catheter (CVC) indwelling.

In this study, the presence of mechanical ventilation as a predisposing factor related to mortality was found significant in hospital acquired *S. maltophilia* infections ($p<0.05$). In a similar study, long-term antibiotic use (>14 days) and urinary catheter presence were found to be significant (3). In another pediatric study, longer hospitalization, septic shock, mechanical ventilation, central vein catheter indwelling, prior use of steroids and carbapenems were related with mortality ($p<0.05$) (5). Ebara et al. (14) found that mechanical ventilation as a risk factor for mortality, similar to this study. In this study, 90% of the patients used broad-spectrum antibiotics and all clinically significant bacteremia episodes were healthcare associated infections. Another study points out that the use of broad-spectrum antibiotics and in particular carbapenems, increases *S. maltophilia* bacteremia (14).

Some studies have reported that initial administration of inappropriate antibacterial treatment was a significant predictor of mortality (16). In our study longer broad-spectrum antibiotic use did not found as a risk factor contrast to many studies (5,14).

Stenotrophomonas maltophilia infection rates has been increasing over recent years (17). Especially the initial condition of the patient is directly related to mortality (18). Also, several virulence factors of *S. maltophilia* such as forming biofilm on surfaces and extracellular enzymes is the cause of its pathogenity (19).

Table 3. Risk factors associated with mortality in *Stenotrophomonas maltophilia* bacteremia patients (67 patients)			
	Mortality (n=11)	No mortality (n=56)	p
Height	8 (73)	32 (57)	0.50
Age (median, month)	25	9	1
Clinics			
Neonatal intensive care unit, n (%)	5 (45)	11 (20)	0.11
Pediatric intensive care unit, n (%)	5 (45)	25 (45)	1
Neonatal and pediatric ICU[a], n (%)	10 (90)	36 (64)	0.15
Hematology oncology clinic, n (%)	1 (10)	11 (20)	0.67
Other pediatric clinics, n (%)	0 (0)	9 (15)	0.34
HA bloodstream infection[b]			
Bakteriyemi (peripheral blood culture), n (%)	5 (45)	11 (27)	0.12
Catheter-associated bacteremia, n (%)	6 (55)	19 (48)	0.31
Comorbidity			
Sepsis, n (%)	6 (55)	28 (50)	1
Respiratory failure, n (%)	2 (18)	14 (25)	1
Heart failure, n (%)	1 (9)	4 (7)	1
Prematurity, n (%)	1 (9)	3 (5)	0.52
Liver failure, n (%)	0 (0)	3 (5)	1
Convulsion, n (%)	1 (9)	2 (4)	0.42
Renal failure, n (%)	0 (0)	1 (2)	1
Diabetic ketoacidosis, n (%)	0 (0)	1 (2)	1
Risk factors			
Central venous catheter, n (%)	6 (66)	29 (52)	1
TPN[c], n (%)	5 (41)	15 (27)	0.28
Neutropenia, n (%)	5 (26)	10 (18)	0.10
Nasogastric tube, n (%)	9 (60)	25 (45)	0.17
Urinary cathater, n (%)	3 (19)	4 (7)	0.08
Mechanical ventilation, n (%)	10 (78)	20 (36)	**0.0016**
Polymicrobial growth detection, n (%)	2 (15)	15 (27)	0.71
Use of broad-spectrum antibiotic, n (%)	11 (100)	49 (88)	0.59
Use of broad-spectrum antibiotic >14 days, n (%)	8 (73)	25 (45)	0.10
Hospital stays longer than 14 days, n (%)	8 (73)	25 (45)	0.10
Immunosuppressive therapy, n (%)	3 (27)	11 (20)	0.69

[a]ICU: Internal care unit, [b]HA: Healthcare-associated, [c]TPN: Total parenteral nutrition

In the SENTRY antmicorbial surveillance programme TMP-SMX resistance to *S. maltophilia* ranging from 2% to %10 (20). In this study, 98% of the *S. maltophilia* bacteremia strains were susceptible to TMP-SMX. Generally, TMP-SMX and fluoroquinolones are the major options for treatment choice. But in some studies minocycline, ceftazidime, ticarcilin-clavunate found susceptible to *S. maltophilia* *in vitro* and used for treatment (14,16). In this study, we used ciprofloxasin and TMP-SMX combination therapy for *S. maltophilia* bacteremia. There are limited data shown that TMP-SMZ combination with levofloxacin or ciprofloxacin had not change the mortality rate of *S. maltophilia* infections (21).

In this study, *S. maltophilia* infection rate was 0.86% (n=67/7764) during the 5-year period. Tokatly Latzer

et al. (5) found the total incidence of *S. maltophilia* isolation during the 5.5-year period was 0.53% and this was lower according to our study.

Sixty-nine percent (n=46) of patients with *S. maltophilia* bacteremia were hospitalized in intensive care units, of which 67% (n=31) were associated with the outbreak. It is determined that the ratio of patient/nurse is over 3 in intensive care units in epidemic periods. It is aimed to avoid the use of CVC, taking care of catheter care and ensuring that the patient/nurse ratio is 2. In addition, it was ensured that only the same patient could use common samples such as heparin bottles or saline. When this is not possible, sterilization methods have been explained and taught. Infection prevention and control trainings were given to all health personnel in the relevant department. It is aimed to repeat these trainings at certain intervals.

Conclusion

In conclusion, nonfermentative gram-negative bacillus such as *S. maltophilia* are important opportunistic pathogens responsible for severe hospital acquired infections. These pathogens are frequently encountered in hospital-associated bloodstream infections especially in intensive care units. In this study, 69% of the patients were hospitalized in intensive care unit. All strains had nosocomial origin. The presence of mechanical ventilation as a predisposing factor related to mortality in patients with hospital acquired *S. maltophilia* bloodstream infections were found to be significant. Monitoring surveillance of antimicrobial susceptibility of these pathogens and optimal treatment are very important for treatment success.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee of Uludağ University on July 10, 2018 with the decision numbered 2018-13/20.

Conflict of Interest: No conflict of interest was declared by the authors.

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