Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20239804 • *J Pediatr Inf 2023;17(2):e99-e107*

Stenotrophomonas maltophilia Bloodstream Infections in Children and Clinical Outcomes of Ceftazidime Treatment

Çocuk Hastalarda *Stenotrophomonas maltophilia* Kan Dolaşım Enfeksiyonları ve Seftazidim Tedavisinin Klinik Sonuçları

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Cite this article as: Güner Özenen G, Akaslan Kara A, Cem E, Yılmaz Çelebi M, Kaçar P, Gülderen M, et al. *Stenotrophomonas maltophilia* bloodstream infections in children and clinical outcomes of ceftazidime treatment. J Pediatr Inf 2023;17(2):e99-e107.

Abstract

Objective: *Stenotrophomonas maltophilia* can cause opportunistic and healthcare-associated infections in hospitalized patients. It differs from other gram-negative pathogens due to intrinsic resistance to various antimicrobials, especially carbapenems. Treatment of *S. maltophilia* infections in children is more challenging than in adults due to possible adverse events of most commonly recommended antimicrobials such as trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones. Studies on the treatment options for *S. maltophilia* infections in children are limited. This study aimed to evaluate the demographic, clinical characteristics, and mortality rates of *S. maltophilia* bloodstream infections (BSI) and identify ceftazidime therapy outcomes.

Material and Methods: A retrospective study was conducted to evaluate pediatric patients with *S. maltophilia* BSI between January 2021 and December 2021. Asymptomatic patients who had positive blood cultures for *S. maltophilia* were excluded because of the possibility of contamination.

Results: A total of 33 patients with *S. maltophilia* BSI were evaluated. Twenty (60.6%) patients were included in the ceftazidime group and 13 (39.4%) patients were included in the other antimicrobials [(TMP-SMX) and ciprofloxacin] group. Median age of the patients was eight months

Öz

Giriş: *Stenotrophomonas maltophilia* hastanede yatan hastalarda fırsatçı veya sağlık hizmeti ilişkili enfeksiyonlara neden olabilir. Başta karbapenemler olmak üzere çeşitli antimikrobiyallere karşı intrinsik dirençli olmaları nedeniyle diğer gram-negatif patojenlerden farklıdırlar. Çocuklarda *S. maltophilia* enfeksiyonlarının tedavisi, trimetoprim-sülfametoksazol (TMP-SMX) ve florokinolonlar gibi en sık önerilen antimikrobiyallerin olası yan etkileri nedeniyle yetişkinlere göre daha zordur. *S. maltophilia* enfeksiyonlarının çocuklarda tedavi seçenekleriyle ilgili çalışmalar sınırlıdır. Bu çalışmada, *S. maltophilia* kan dolaşımı enfeksiyonu (KDE) olan çocuk hastaların demografik özelliklerini, klinik özelliklerini, ölüm oranlarını ve seftazidim tedavisinin sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2021-Aralık 2021 tarihleri arasında *S. maltophilia* KDE olan çocuk hastalar retrospektif olarak değerlendirildi. Kan kültüründe *S. maltophilia* üremesi olmasına rağmen asemptomatik olan hastalar kontaminasyon olasılığı nedeniyle çalışmadan çıkarıldı.

Bulgular: *S. maltophilia* KDE olan toplam 33 hasta değerlendirildi. Yirmi (%60.6) hasta seftazidim grubuna, 13 (%39.4) hasta diğer antimikrobiyal tedavi [(TMP-SMX) ve siprofloksasin] grubuna dahil edildi. Hastaların or-

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Received: 14.03.2022 **Accepted:** 18.07.2022 **Available Online Date:** 23.06.2023

(three days-17.5 years). The most common underlying disease was congenital heart disease (27.3%), followed by chronic neurological/neuromuscular disorders (18.2%) and esophageal atresia (9.1%). Twenty-five (78.8%) patients had a central venous catheter, 14 (42.6%) patients had surgery, and 29 (87.9%) patients had a history of prior pediatric intensive care unit admission. Prior antimicrobial treatment was administered to 26 (78.8%) patients before BSI onset. The rates of ceftazidime, ciprofloxacin, levofloxacin, and TMP-SMX susceptibility were 83.9%, 93.3%, 93.5%, and 65.6%, respectively. In the ceftazidime group, clinical success rate was 93.8% and there were no deaths within 30 days. In the other antimicrobials group, clinical success rate was 84.6% and two patients died within 14 days. However, there were no statistically significant differences in clinical success and mortality rates between groups.

Conclusion: *S. maltophilia* has intrinsic resistance to carbapenems and other antimicrobials, and treatment options for these infections are limited. We suggest that ceftazidime could be an alternative antimicrobial agent in pediatric patients with *S. maltophilia* BSI when other options could not be used.

Keywords: Ceftazidime, *Stenotrophomonas maltophilia*, pediatric

tanca yaşı sekiz ay (üç gün-17.5 yıl) idi. Altta yatan en sık hastalık konjenital kalp hastalığı (%27.3) idi, bunu kronik nörolojik/nöromüsküler hastalıklar (%18.2) ve özofagus atrezisi (%9.1) izledi. Yirmi beş (%78.8) hastada santral venöz kateter, 14 (%42.6) hastada cerrahi operasyon öyküsü ve 29 (%87.9) hastada daha önce pediyatrik yoğun bakıma yatış öyküsü vardı. *S. maltophilia* KDE öncesi 26 (%78.8) hasta antimikrobiyal tedavi almaktaydı. Seftazidim, siprofloksasin, levofloksasin ve TMP-SMX duyarlılık oranları sırasıyla %83.9, %93.3, %93.5 ve %65.6 idi. Seftazidim grubunda klinik yanıt oranı %93.8 idi ve 30 gün içinde ölüm görülmedi. Diğer antimikrobiyal grubunda klinik yanıt oranı %84.6 idi ve 14 gün içinde iki hasta öldü. Bununla birlikte, gruplar arasında klinik yanıt ve ölüm oranlarında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: *S. maltophilia*, karbapenemlere ve diğer birçok antimikrobiyale karşı intrinsik dirence sahiptir ve bu nedenle enfeksiyonlarda tedavi seçenekleri sınırlıdır. Seftazidim, *S. maltophilia* KDE olan pediyatrik hastalarda diğer seçeneklerin kullanılamadığı durumlarda alternatif bir antimikrobiyal ajan olarak kullanılabilir.

Anahtar Kelimeler: Seftazidim, *Stenotrophomonas maltophilia*, pediyatrik

Introduction

Stenotrophomonas maltophilia is an aerobic, biofilm-forming, non-fermentative, gram-negative bacterium in hospital and community settings that can cause opportunistic and healthcare-associated infections in hospitalized patients (1). It is not a part of normal human flora and lives in humid environments such as sink drains, showerheads, nebulizers, mechanical ventilators, and endoscopes (2). *S. maltophilia* is generally considered a low-virulence organism in healthy populations (3,4). Immunosuppression, underlying malignancy, intensive care unit admission, mechanical ventilation, having a central venous catheter, prior antimicrobial therapy (especially meropenem), prolonged hospitalization, cystic fibrosis, and prolonged neutropenia have all been defined as risk factors for *S. maltophilia* infections (1-6). Previous studies have reported mortality rate in *S. maltophilia* bloodstream infections (BSI) as high as 30-40.6% in hospitalized children (7-10).

Stenotrophomonas maltophilia differs from the other gram-negative pathogens due to intrinsic resistance to various antimicrobials, especially carbapenems (5). Therefore, these infections cause a major therapeutic challenge for clinicians due to limited treatment options (6). Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended as the first drug of choice for treating *S. maltophilia* infections as monotherapy or a part of combination therapy (2,3). Ciprofloxacin, levofloxacin, ceftazidime, tigecycline, and minocycline, alone or combined with other antibiotics, may be considered an alternative to TMP-SMX (2,5,6,11). However, treatment of *S. maltophilia* infections in children is more challenging than in adults due to possible adverse events of most commonly recommended antimicrobials such as TMP-SMX and fluoroquinolones. Other less toxic antimicrobial options are poorly studied in the pediatric population (2,10). Cephalosporins' low activity against *S. maltophilia* and high resistance rates limit their empirical use in the treatment of these infections (12). Cephalosporins have the risk of resistance induction due to β-lactamase production and low β-lactam activity. However, cefoperazone, ceftazidime, and cefepime show higher in vitro activity than other cephalosporins (13,14).

This study aimed to evaluate the demographic, clinical characteristics, and mortality rates of *S. maltophilia* BSI and the impact of ceftazidime therapy on the outcomes as an alternative antimicrobial agent to TMP-SMX and fluoroquinolones.

Materials and Methods

Study Design and Study Population

A retrospective descriptive study was performed between January 2021-December 2021. Our hospital is a referral center for pediatric patients, including a neonatal intensive care unit, pediatric intensive care unit, pediatric hematology-oncology, immune deficiency, bone marrow transplantation, pediatric surgery, and pediatric cardiovascular surgery department. All hospitalized patients younger than 18 years old with positive peripheral blood and/or catheter cultures for *S. maltophilia* were evaluated. The patients were retrospectively identified through medical records. A standardized form was used to collect epidemiologic data, including demographic characteristics, underlying medical conditions, invasive procedures, and laboratory findings including antimicrobial susceptibility, treatment, and prognosis. Patients older than 18 years old and asymptomatic patients who had positive blood cultures for *S. maltophilia* were excluded because of the possibility of contamination. Contamination was defined as asymptomatic patients with positive blood cultures for *S. maltophilia* whose bacteremia resolved without treatment, and a negative culture confirmed that. The patients were classified into two groups according to antimicrobial therapy: ceftazidime group and other antimicrobials (TMP-SMX and ciprofloxacin) group.

Microbiologic Methods

Blood samples for blood cultures were inoculated in BACTEC 9240 Culture Media (Becton-Dickinson, Diagnostic Instrument System, Sparks, USA) and loaded into BACTEC 9240 automated instruments (Becton-Dickinson, Diagnostic Instrument. System, Sparks, USA). Inoculated bottles were incubated for seven days or until they were positive. Identification and analysis of the antimicrobial susceptibilities of the detected bacteria for TMP-SMX were carried out using the VITEK 2 (bioMérieux, France) automated system and evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (15). Additionally, susceptibility testing for levofloxacin (LEV), ciprofloxacin (CIP), ceftazidime (CAZ), and of all bacterial isolates by disk diffusion tests were performed according to Clinical and Laboratory Standards Institute (CLSI) criteria. If zone diameters were not available for *S. maltophilia* in the CLSI, zone diameters were interpreted according to the defined limit values for *Pseudomonas* spp (16).

Definitions

Stenotrophomonas maltophilia BSI was defined if isolates were isolated from one or more blood samples obtained from a central and/or peripheral vein (or other vascular access) and if the patient had clinical symptoms compatible with the infection (1). Neutropenia was defined as an absolute neutrophil count of $<1.5 \times 10^9$/L, and thrombocytopenia was defined as a platelet count of $<150 \times 10^9$/L. Prior antimicrobial treatment was defined as using antimicrobials within 14 days before the onset of BSI. Previous immunosuppressive therapy was defined as the use of immunosuppressive therapy within one month before the onset of BSI. Surgery was defined as a surgical procedure that was performed within one month of the onset of BSI. Clinical success was defined as the resolution of all attributable signs, symptoms, and laboratory abnormalities related to *S. maltophilia* BSI and as the clearance of microbiological culture.

Statistical Analysis

The descriptive statistical analysis was performed using SPSS statistical software (version 22; SPSS, Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables or percentages for categorical variables. Categorical variables are expressed as numbers (n) and percentages (%). Student's t-test was used to compare continuous parametric variables, Mann-Whitney U test was used to compare continuous nonparametric variables, and categorical variables were compared using Pearson $\chi 2$ or Fisher's exact tests. A p value of ≤ 0.05 was considered statistically significant.

This study was approved by the local ethics committee (Decision no: 2022105-02, Date: 10.03.2022).

Results

Demographic, Clinical, and Laboratory Data

From medical records, we identified a total of 44 pediatric patients with positive *S. maltophilia* blood cultures. Of the 44 cases, 11 patients were excluded since their isolates were considered as contamination. The remaining 33 patients with *S. maltophilia* BSI were included in our study. Twenty (60.6%) patients were included in the ceftazidime group and 13 (39.4%) patients were included in the other antimicrobials group. In the ceftazidime group, ceftazidime was given to sixteen patients as monotherapy, three as combination with TMP-SMX, and one as combination with ciprofloxacin. In the other antimicrobials group, nine patients were given TMP-SMX as monotherapy, two patients were given ciprofloxacin as monotherapy, and one patient was given TMP-SMX plus ciprofloxacin as a combination.

In the ceftazidime group, median age of the patients was 14 months (three days–16.5 years), and 45% (n= 9) of them were males. The most common underlying disease was congenital heart disease (30%, n= 6), followed by chronic neurological/neuromuscular disorders (15%, n= 3) and esophageal atresia (10%, n= 2). *S. maltophilia* infections were most common in the pediatric intensive care unit (ICU) (35%, n= 7), followed by cardiovascular surgery ICU (25%, n= 5) and neonatal ICU (15%, n= 3). Median duration of hospitalization before the onset of BSI was nine (1-182) days, and median total length of hospital stay was 43 (14-203) days. Thirteen (65%) patients had a central venous catheter, ten (50%) patients required mechanical ventilation, four (20%) required a high flow nasal cannula, fourteen (70%) patients had a nasogastric tube, and seven (35%) patients had a urinary catheter. Surgery was performed in eight (40%) patients, and eighteen (90%) patients had a prior pediatric ICU admission history. Prior antimicrobial treatment was administered to sixteen (80%) patients before the onset of *S. maltophilia* BSI. The most common prior antimicrobial treatment was glycopeptides (35%), followed by carbapenems (30%), piperacillin-tazobactam (15%), ampicillin-sulbactam (20%), and aminoglycosides (15%). Median duration of prior antimicrobial treatment was seven (1-16) days. Two (10%) patients had concomitant bacteremia or fungemia. Seventeen patients (85%) had hospital-acquired infections, and three (15%) had community-acquired infections. Ten (50%) patients had fever, one (5%) patient was neutropenic, and five (25%) were thrombocytopenic.

In the other antimicrobials group, median age of the patients was four months (1.5 months-17.5 years), and 76.9% (n= 10) of them were males. The most common underlying disease was congenital heart disease (23.1%, n= 3) and chronic neurological/neuromuscular disorders (23.1%, n= 3). *S. maltophilia* infections were most common in the pediat-

ric intensive care unit (ICU) (38.5%, n= 5), followed by pediatric infectious disease ward (30.8%, n= 4) and neonatal ICU (23.1%, n= 3). Median duration of hospitalization before the onset of BSI was 28 (6-72) days, and median total length of hospital stay was 55 (11-219) days. Twelve (92.3%) patients had a central venous catheter, seven (53.8%) patients required mechanical ventilation, three (23.1%) required a high flow nasal cannula, ten (76.9%) patients had a nasogastric tube, and five (38.5%) patients had a urinary catheter. Surgery was performed in six (46.2%) patients, and eleven (84.6%) patients had a prior pediatric ICU admission history. Prior antimicrobial treatment was administered to ten (76.9%) patients before the onset of *S. maltophilia* BSI. The most common prior antimicrobial treatment was carbapenems (46.2), followed by glycopeptides (38.5%) and piperacillin-tazobactam (23.1%). Median duration of prior antimicrobial treatment was 13.5 (2-28) days. Five (38.5%) patients had concomitant bacteremia or fungemia. All patients had hospital-acquired infections. Seven (53.8%) patients had fever, two (15.4%) patients were neutropenic, and six (46.2%) were thrombocytopenic.

When considering age and sex, there were no statistical differences between the groups (p= 0.650 and 0.070). No statistical differences for the length of hospital stay following the onset of infection and negative culture time between the groups were seen (p= 0.074 and 0.107). When health care interventions were evaluated, there was no statistical difference between the groups for the nasogastric tube, mechanical ventilator, tracheostomy, high flow nasal cannula, urinary catheter, central venous catheter, and history of surgery (p> 0.05). Prior antibiotic treatment, immunosuppressive therapy, and duration of prior antimicrobial treatment duration were not statistically different between the groups (p values were 0.833, 0.052, and 0.182, respectively). No statistical differences for neutropenia and thrombocytopenia between the groups were seen (p= 0.547 and 0.208). Concomitant bacteremia or fungemia, central venous catheter removal, clinical success rate, and 14-day mortality rate were not statistically different between the groups (p values were 0.084, 0.561, 0.513, and 0.148, respectively). Table 1 summarizes the demographic and clinical characteristics of the study population.

In all groups, median white blood cell count was 11.4 (0.07-21) x 10^9/L, median absolute neutrophil count was 6.5 (0.01-18) x 10^9/L, median platelet count was 209 (9-559) x 10^9/L, and median value of C-reactive protein was 4.04 (0.06-32.87) mg/dL.

Antimicrobial Susceptibility, Treatment, and Outcomes

The rate of ceftazidime resistance was 12.9%, TMP-SMX resistance was 6.3%, ciprofloxacin resistance was 3.3% and levofloxacin resistance was 3.2%. Table 2 summarizes *S. maltophilia* antimicrobial susceptibility of the study population.

In the ceftazidime group, in sixteen patients, ceftazidime was administered as monotherapy, and clinical response was achieved in fifteen (93.8%) patients. In one patient, ceftazidime monotherapy was ineffective and was switched to ciprofloxacin due to persistent bacteremia. This patient had recurrent culture positivity, and due to lack of vein access, her central venous catheter could not be removed. Median negative culture time was seven (5-39) days, and total treatment duration was 14 (5-32) days. In three patients, ceftazidime plus TMP-SMX was administered, and clinical response was achieved in two (66.7%) patients. In one patient, the ceftazidime plus TMP-SMX combination was ineffective, and TMP-SMX was switched to ciprofloxacin due to TMP-SMX resistance. Median negative culture time was seven (5-9) days, and total treatment duration was 14 (7-19) days. In one patient, ceftazidime plus ciprofloxacin was administered as a combination, and clinical response was achieved. Of all thirteen central venous catheters, eight (61.5%) were removed during the treatment of *S. maltophilia* BSI. Median duration of catheter removal was nine (1-24) days. Negative culture time was eight days, and total treatment duration was 14 days. Echocardiography was performed in 14 (70%) patients, and there was no vegetation. There were no attributable or total deaths within 30 days in the study group.

In the other antimicrobials group, in nine patients, TMP-SMX was administered as monotherapy, and clinical response was achieved in nine (90%) patients. One patient receiving TMP-SMX died on the sixth day of the treatment. This patient had concomitant bacteremia with *Pseudomonas aeruginosa*, and due to lack of vein access, his central venous catheter could not be removed. Median negative culture time was four (1-9) days, and total treatment duration was 14 (5-21) days. In two patients, ciprofloxacin was administered as monotherapy, and clinical response was achieved in all (100%) patients. Median negative culture time was 7.5 (3-12) days, and total treatment duration was 18.5 (14-23) days. In one patient, TMP-SMX plus ciprofloxacin was administered as a combination, and the patient died on the 10th day of the treatment. This patient had a concomitant fungemia with *Candida krusei*, and due to lack of vein access, his central venous catheter could not be removed. Of all twelve central venous catheters, six (50%) were removed during the treatment of *S. maltophilia* BSI. Median duration of catheter removal was one (1-14) days. Echocardiography was performed in nine (69.2%) patients, and there was no vegetation. The attributable (14-day mortality) rate was 15.4% in the other antimicrobials group. Table 3 summarizes the outcomes of ceftazidime treatment in *S. maltophilia* bloodstream infections.

Table 1. The demographic and clinical characteristics of the study population

Characteristics	All patients	Ceftazidime group[a]	Other antimicrobials group[b]	p
Patients, n (%)	33 (100)	20 (60.6)	13 (39.4)	
Age, months, median (range)	8 (3 days- 17.5 years)	14 (3 days- 16.5 years)	4 (1.5 months- 17.5 years)	0.650
Sex, male, n (%)	19 (57.6)	9 (45)	10 (76.9)	0.070
Days of hospitalization before the onset of BSI, median (range)	15.5 (1-181)	9 (1-181)	28 (6-72)	0.074
Days of hospitalization after the onset of BSI, median (range)	26 (2-164)	26 (8-128)	33 (2-164)	0.866
The total length of hospital stay, days, median (range)	46 (11-219)	43 (14-203)	55 (11-219)	0.497
Underlying conditions, n (%)				
Congenital heart disease	9 (27.3)	6 (30)	3 (23.1)	
Chronic neurological/neuromuscular disorder	6 (18.2)	3 (15)	3 (23.1)	
Esophageal atresia	3 (9.1)	2 (10)	1 (7.7)	
Chronic lung disease	1 (3)	1 (5)	0 (0)	
Prematurity	1 (3)	1 (5)	0 (0)	
Pneumonia	2 (6.1)	1 (5)	1 (7.7)	
Ichthyosis	1 (3)	1 (5)	0 (0)	
Metabolic disease	1 (3)	1 (5)	0 (0)	
COVID-19	1 (3)	1 (5)	0 (0)	
MIS-C	1 (3)	1 (5)	0 (0)	
Genetic syndrome	1 (3)	1 (5)	0 (0)	
Chronic renal failure	1 (3)	1 (5)	0 (0)	
Hematologic-solid malignancy	2 (6)	0 (0)	2 (15.4)	
Congenital diaphragmatic hernia	1 (3)	0 (0)	1 (7.7)	
Burn	1 (3)	0 (0)	1 (7.7)	
Primary immunodeficiency	1 (3)	0 (0)	1 (7.7)	
Ward type of admission, n (%)				
Pediatric ICU	12 (36.3)	7 (35)	5 (38.5)	
Cardiovascular surgery ICU	6 (18.2)	5 (25)	1 (7.7)	
Neonatal ICU	7 (21.2)	4 (20)	3 (23.1)	
Pediatric infectious disease	8 (24.3)	4 (20)	4 (30.8)	
Fever, n (%)	17 (51.5)	10 (50)	7 (53.8)	0.829
Neutropenia (<1.5 x 10^9/L), n (%)	3 (9.1)	1 (5)	2 (15.4)	0.547
Thrombocytopenia, (<150 x 10^9/L), n (%)	11 (33.3)	5 (25)	6 (46.2)	0.208
Prior pediatric ICU admission, n (%)	29 (87.9)	18 (90)	11 (84.6)	0.643
Nasogastric tube, n (%)	24 (72.7)	14 (70)	10 (76.9)	0.663
Central venous catheter, n (%)	25 (78.8)	13 (65)	12 (92.3)	0.074
Mechanical ventilator, n (%)	17 (51.5)	10 (50)	7 (53.8)	0.829
History of surgery, n (%)	14 (42.4)	8 (40)	6 (46.2)	0.727
Urinary catheter, n (%)	12 (36.3)	7 (35)	5 (38.5)	0.840
HFNC, n (%)	7 (21.2)	4 (20)	3 (23.1)	0.833
Tracheostomy, n (%)	1 (3)	0 (0)	1 (7.7)	0.394
Total parenteral nutrition, n (%)	3 (9.1)	0 (0)	3 (23.1)	0.052
Immunosuppressive therapy, n (%)	3 (9.1)	0 (0)	3 (23.1)	0.052
Concomitant bacteremia or fungemia, n (%)	7 (21.2)	2 (10)	5 (38.5)	0.084

Table 1. The demographic and clinical characteristics of the study population (continue)

Characteristics	All patients	Ceftazidime group[a]	Other antimicrobials group[b]	p
Prior antimicrobial treatment, n (%)	26 (78.8)	16 (80)	10 (76.9)	0.833
Glycopeptides	12 (36.4)	7 (35)	5 (38.5)	
Carbapenems	12 (36.4)	6 (30)	6 (46.2)	
Ampicillin-sulbactam	5 (15.2)	4 (20)	1 (7.7)	
Piperacillin/tazobactam	6 (18.2)	3 (15)	3 (23.1)	
Aminoglycosides	3 (9.1)	3 (15)	0 (0)	
Cephalosporins	3 (9.1)	2 (10)	1 (7.7)	
Quinolones	1 (3)	0 (0)	1 (7.7)	
Tigecycline	0 (0)	0 (0)	0 (0)	
Colistin	1 (3)	0 (0)	1 (7.7)	
Trimethoprim-sulfamethoxazole		0 (0)	0 (0)	
Duration of prior antimicrobial treatment, days, median, (range)	7 (1-28)	7 (1-16)	13.5 (2-28)	0.182
Central venous catheter removal, n (%)	14 (56)	8 (61.5)	6 (50)	0.561
Central venous catheter removal duration, days, median, (range)	6.5 (1-24)	9 (1-24)	1 (1-14)	0.108
Negative culture time, days, median, (range)	5 (1-39)	7 (5-39)	4 (1-6)	0.107
Clinical success, n (%)	29 (87.9)	15 (93.8)[c]	11 (84.6)	0.513
14-day mortality, n (%)	2 (6.1)	0 (0)	2 (15.4)	0.148
30-day mortality, n (%)	2 (6.1)	0 (0)	2 (15.4)	0.148

ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, MIS-C: Multisystem inflammatory syndrome in children, HFNC: High flow nasal cannula, TMP-SMX: Trimethoprim-sulfamethoxazole.
[a]In sixteen patients, ceftazidime was administered as a monotherapy, in three patients, ceftazidime plus TMP-SMX was administered, and in one patient, ceftazidime plus ciprofloxacin was administered as a combination.
[b]In nine patients, TMP-SMX was administered as a monotherapy, in two patients, ciprofloxacin was administered as a monotherapy, and in one patient, TMP-SMX plus ciprofloxacin was administered as a combination.
[C]In statistical analysis, only sixteen patients in which ceftazidime was administered as monotherapy were evaluated.

Table 2. *Stenotrophomonas maltophilia* antimicrobial susceptibility of the study population

Antimicrobial agents	Total number of isolates	Susceptible, n (%)	Intermediate, n (%)	Resistant, n (%)
Trimethoprim-sulfamethoxazole	32	21 (65.6)	9 (27.3)	2 (6.3)
Ceftazidime	31	26 (83.9)	1 (3.2)	4 (12.9)
Ciprofloxacin	30	28 (93.3)	1 (3.3)	1 (3.3)
Levofloxacin	31	29 (93.5)	1 (3.2)	1 (3.2)

Discussion

In this study, we evaluated 33 pediatric patients with *S. maltophilia* BSI, and similar to the literature, 87.9% of the patients had a history of ICU admission, and 78.8% had prior antimicrobial treatment. Contrary to previous reports, the rate of TMP-SMX susceptibility was lower (65.6%), and the rate of ceftazidime susceptibility was higher (83.9%) in our study. We found clinical success rates of ceftazidime monotherapy to be 93.8% and ceftazidime plus TMP-SMX combination to be 66.7%. In the ceftazidime group, within 30 days, there were no attributable or total deaths. In the other antimicrobials group, clinical success rate was 84.6% and two patients died within 14 days. However, there were no statistically significant differences in clinical success and mortality rates between the groups.

Stenotrophomonas maltophilia is an emerging pathogen that contributes to high morbidity and mortality due to limited antimicrobial treatment options (1,2). It has intrinsic resistance to many antimicrobials, making TMP-SMX the first drug of choice (5,11,17). The increasing rate of TMP-SMX or quinolones resistant isolates and the possibility of adverse events or intolerance in children, which were not observed at the adults, lead clinicians to a major challenge in the therapy of *S. maltophilia* infections (11,12). For instance, TMP-SMX is associated with an increased risk of bilirubin displacement and kernicterus in premature infants (18). Quinolones are associated with collagen degradation and musculoskeletal ad-

Table 3. Outcomes of ceftazidime treatment in *Stenotrophomonas maltophilia* bloodstream infections

Antimicrobial	Number of patients	Clinical success	Treatment not effective	Negative culture time, days, median (min-max)	Treatment duration, days, median, (min-max)	14-day mortality, n (%)	30-day mortality, n (%)	Treatment change
Ceftazidime	16	15 (93.8)	1 (7.2)	5 (2-27)	14 (5-32)	0 (0)	0 (0)	In one patient, ceftazidime switched to ciprofloxacin
Ceftazidime + TMP-SMX	3	2 (66.7)	1 (33.3)	7 (5-9)	14 (7-19)	0 (0)	0 (0)	In one patient TMP-SMX switched to ciprofloxacin
Ceftazidime + ciprofloxacin	1	1 (100)	0 (0)	8	14	0 (0)	0 (0)	None
TMP-SMX	10	9 (90)	1 (10)	4 (1-9)	14 (5-21)	1 (10)	9 (90)	None
Ciprofloxacin	2	2 (100)	0 (0)	7.5 (3-12)	18.5 (14-23)	0 (0)	0 (0)	None
TMP-SMX + ciprofloxacin	1	0 (0)	1 (100)	No negative culture	10	1 (100)	1 (100)	TMP-SMX added to ciprofloxacin due to treatment failure

TMP-SMX: Trimethoprim-sulfamethoxazole.

verse events in children (19). However, studies on the treatment options for these infections are limited in the pediatric population (3). In this study, we evaluated the outcomes of ceftazidime treatment in the pediatric population, including neonates with *S. maltophilia* BSI.

In a recent study, Furuichi et al. have evaluated 19 children with *S. maltophilia* bacteremia and reported TMP-SMX susceptibility as 100% and ceftazidime susceptibility as 37% (4). They have shown that the use of carbapenems within seven days before the onset of bacteremia and a previous intensive care unit stay are significantly associated with *S. maltophilia* bacteremia. Consistent with their results, in our study, 87.9% of the patients had a history of ICU admission, and 78.8% had prior antimicrobial treatment. In another study, Aydın et al. have evaluated 48 pediatric patients with *S. maltophilia* bacteremia (10). Among these isolates, 90% were susceptible to TMP-SMX, and 94% were susceptible to ciprofloxacin. However, different from the previous studies, the rate of TMP-SMX susceptibility was lower (65.6%), and ceftazidime susceptibility was higher (83.9%) in our study.

Alsuhaibani et al. have evaluated 68 pediatric patients with *S. maltophilia* bacteremia (1). The reported seven-day mortality rate is 33.8%. They have also noted that there was no statistical difference in mortality rates in patients who received TMP-SMX as monotherapy or in combination with other antibiotics (fluoroquinolone, ceftazidime, or an aminoglycoside). Büyükçam et al. have evaluated 20 isolates from 12 pediatric patients with *S. maltophilia* bacteremia (9). In their study, the most commonly used antimicrobial agent is ciprofloxacin, and they have reported a mortality rate of 33.3%. Contrary to these reports, in our study, all patients received ceftazidime as monotherapy or combination, and there was no death. Only two patients died in the other antimicrobials and group and it was not statistically different than the ceftazidime group. However, in all of the studies, as well as in our study, the patients' characteristics and underlying diseases were not homogenous.

Andelković et al. have reviewed 260 adult and pediatric patients with *S. maltophilia* infections (5). They have reported that TMP-SMX was the most frequently used antibiotic in the treatment (33.8%), followed by ceftazidime (24.2%), ciprofloxacin (20.4%), amikacin (14.2%), tobramycin, and imipenem (12.3%). Adverse drug reactions have been observed in six patients with fluoroquinolones or TMP-SMX (5). They have shown that ceftazidime is used with other antibiotics in most studies and that such treatment is highly efficient (5). Due to limited clinical data, they have suggested that treatment with ceftazidime could be a therapeutic choice in patients with allergies or resistance to TMP-SMX, which was also supported by our study.

Resistance in *S. maltophilia* can occur through a variety of mechanisms, including -lactamase production, Qnr gene expression, the presence of class 1 integrons and multidrug-efflux pump genes, low membrane permeability, and phenotypic and genotypic variability (5,13). Ceftazidime may be inhibited by the production of intrinsic beta-lactamases L1 and L2 and overexpression efflux pumps, which reduce the intracellular concentration of the drug (11). There are no guide-

lines for the treatment of *S. maltophilia* infections in pediatric populations. Treatment recommendations are based on the results of in vitro susceptibility studies, case series, or expert opinion (5,15). Studies have shown that TMP-SMX is the most effective antimicrobial against *S. maltophilia* (3,5,12). Other alternative therapy options include fluoroquinolones, ceftazidime, minocycline, tigecycline, ticarcillin-clavulanate, cefiderocol, ceftazidime-avibactam, and aztreonam (3,11). However, monotherapy or antimicrobial combinations for treating *S. maltophilia* infections remain controversial (14). Infectious Diseases Society of America Guidance does not suggest ceftazidime for the treatment of *S. maltophilia* infections either as monotherapy or as a component of combination therapy as an expert opinion. They note that intrinsic β-lactamases produced by *S. maltophilia* are likely to render ceftazidime ineffective (15). In contrast, we showed a 93.8% clinical response with ceftazidime monotherapy and 66.7% with ceftazidime plus TMP-SMX in *S. maltophilia* BSI.

Wang et al. have evaluated 128 pediatric patients with *S. maltophilia* infections from various isolates (6). They have shown that ceftazidime showed antibacterial activity against the bacteria. Therefore, they suggest that the third-generation cephalosporins can be used as alternative drugs for patients who can not tolerate TMP-SMX. Falagas et al. have reviewed 49 adult and pediatric patients with various *S. maltophilia* infections (11). They have reported 24.5% of the patients were treated with ceftriaxone or ceftazidime monotherapy or combination with other antibiotics, and the clinical success rate was 66.7%. They have noted that this data suggests that ceftazidime or ceftriaxone, alone or in combination with other antibiotics, may be considered as alternative options beyond TMP-SMX. Similar to these studies, our results suggest that ceftazidime can be an alternative treatment option, especially for infants and neonates with S. *maltophilia* BSI.

This study had limitations, including its retrospective nature and a lack of the advantages of randomized control studies. In addition, the sample size is relatively small. Resistance patterns and, therefore, response to treatment might change from one institution to another; thus, it is difficult to generalize our findings. However, our study gives additional information about using ceftazidime as an alternative drug, especially in infants and neonates where other drugs of choice could not be used.

Due to the intrinsic resistance of *S. maltophilia* to carbapenems and other antimicrobials, treatment options for these infections are limited. The use of ceftazidime alone in *S. maltophilia* infections, even if it is susceptible in vitro, has the risk of resistance induction due to β-lactamase production. We suggest that ceftazidime could be an alternative antimicrobial agent in pediatric patients with *S. maltophilia* BSI in special populations like neonatal period or the risk of adverse events when other options could not be used. Further and larger prospective case-control studies to evaluate the outcomes of ceftazidime therapy in *S. maltophilia* infections are recommended.

Ethics Committe Approval: Ethics committee approval for the study was obtained from İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2022105-02, Date: 10.03.2022).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- İD; Design- İD, GGÖ; Supervision- İD, NB, AB, HA; Resources- GGÖ, SA, MK, AB, PK; Data Collection and/or Processing- GGÖ, AAU, HA, EC, MYC, PU, ME, MU, SA; Analysis and/or Interpretation- GGÖ, AAK, EC, MYÇ, PK; Literature Search - GGÖ, MG; Writing- GGÖ, İD; Critical Review- Tüm yazarlar

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

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