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ORIGINAL ARTICLE

Risk factors and clinical characteristics of *Stenotrophomonas maltophilia* infections in neonates

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Background: The aim of this study was to review the risk factors and clinical, bacteriological, and epidemiological characteristics of *Stenotrophomonas maltophilia* infections in our neonatal intensive care unit.
Methods: A retrospective matched case–control study was performed by comparing 23 cases of *S maltophilia* with 45 controls to identify the potential risk factors. To identify the case patients, the admission and medical records of patients in the neonatal intensive care unit and records from the Microbiology Department were reviewed between 2003 and 2008.
Results: Sepsis in two neonates (9%), conjunctivitis in two neonates (9%), and ventilator-associated pneumonia in 19 (82%) neonates were determined. Invasive-procedures, exposure to aminoglycoside and carbapenem, total parenteral nutrition, histamine 2 blockers, exposure to steroids, cholestasis, and duration of hospitalization were significantly associated with *S maltophilia* infections ($p < 0.05$). On multivariate analysis, invasive procedures (odds ratio, 18.81) and duration of hospitalization (odds ratio, 1.06) were determined to be the risk factors for *S maltophilia* infection. The most active antimicrobial agent was trimethoprim/sulfamethoxazole (87%) for *S maltophilia* infection, and the mortality rate was 17%.
Conclusions: Neonatologists should avoid from unnecessary invasive procedures and broad-spectrum antibiotics to reduce *S maltophilia* infections. Invasive procedures should be finished in the shortest time possible. Agent/factor-specific antibacterial treatment should be administered. Patients being discharged as early as possible will also reduce infection

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frequency. *Stenotrophomonas maltophilia* should be considered in patients with high *Stenotrophomonas* infection risk factors.

Introduction

Stenotrophomonas maltophilia is a multidrug-resistant, non-fermenting, aerobic, gram-negative bacillus that is generally regarded an as opportunistic pathogen. It is an important nosocomial pathogen observed with increasing frequency.[1–3] *Stenotrophomonas maltophilia* causes hospital-acquired infections, such as pneumonia, bacteremia, endocarditis, and central nervous system, ophthalmological, urinary tract, bone and joint, skin and soft tissue, and gastrointestinal infections, and is occasionally associated with septic shock in critically ill and immunosuppressed patients.[1–3] Most of the clinical studies dealing with *S maltophilia* have focused on the adult population, and only a few studies have examined the risk factors for *S maltophilia* in newborns and children.[3–5] The aim of this study was to review the risk factors and clinical, bacteriological, and epidemiological characteristics of *S maltophilia* infections in our neonatal intensive care unit (NICU) between January 2003 and August 2008.

Materials and methods

Patient and control identification

This retrospective matched case–control study was carried out in neonates with *S maltophilia* infections at the Karadeniz Technical University NICU between 2003 and 2008. To identify the case patients, we reviewed the admission and medical records of patients in the NICU and records from the Microbiology Department in the study period. Control patients were selected from the patients who stayed in the NICU for at least 72 hours and had neonatal pneumonia and/or nosocomial sepsis caused by pathogens other than *S maltophilia*. To determine the risk factors for *S maltophilia* infections among neonates, 23 case patients were compared with 45 control patients. Medical charts of all infants with positive cultures for *S maltophilia* and control cases were reviewed for birth weight; gestational age; delivery type; postnatal age at hospitalization; prolonged rupture of membranes; invasive procedures (mechanical ventilation, intubation, urinary catheter, umbilical catheter); duration of mechanical ventilation (day); exposure to antimicrobial agents (aminoglycosides, carbapenems, cephalosporins, penicillins); administration of total parenteral nutrition (TPN); duration of TPN; histamine 2 (H2) blockers; exposure to steroids; cholestasis; elevated liver enzymes; death; sepsis-related death; and duration of hospitalization. All the risk factors for infection were calculated before the onset of infection in both groups.

Definitions

Sepsis was considered in the presence of two or more of the following criteria associated with positive blood culture: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea or hyperventilation, and (4) abnormal white blood cells or an increase in immature forms. Septic shock was defined as refractory hypotension despite adequate fluid resuscitation and cardiac output.[6] Ventilator-associated pneumonia (VAP) was defined as an infection in a newborn requiring at least 48 hours of mechanical ventilation and developing new and persistent radiographic evidence of focal infiltrates 48 hours or more after the initiation of mechanical ventilation.[7] Conjunctivitis was defined as the presence of a purulent ocular discharge, erythema, and edema of the lids.

Preterm labor was defined as onset labor before 37 weeks' gestation. Prolonged rupture of membranes was defined as rupture of membranes 18 hours or more before delivery. Cholestasis was defined as direct bilirubin level greater than 2 mg/dL. Hypoalbuminemia was taken as a serum albumin level lower than 3 g/dL. Death was regarded as *S maltophilia* related if it occurred within 7 days of the positive culture and if clinical signs and symptoms of the infections were documented in the medical record when the patient died.

The presence of an umbilical venous catheter was included as a risk factor only if inserted before the onset of infection and in place at the time of a positive culture result. Surgery was included only if the procedure was performed 7 days or less before the onset of infection. Urinary catheter, TPN, and H2 blockers were accepted as a risk factor only if these parameters were applied to patients within one week before the isolation of *S maltophilia*. Cholestasis and elevated liver enzymes were accepted as risk factors, only if they are present at the time a positive culture was obtained. Previous antimicrobial (penicillin, aminoglycoside, cephalosporin, and carbapenem) and steroid therapies were recorded within 2 weeks before the isolation of *S maltophilia*.

Microbiology

Stenotrophomonas maltophilia isolates were identified using conventional tests and the Phoenix Automated Microbiology System (Becton Dickinson Diagnostic Systems, Sparks, Maryland, USA). Antimicrobial susceptibility tests were performed using Phoenix GN Combo Panels (Becton Dickinson Diagnostic Systems) (combined identification and susceptibility cards) and interpreted as described by the Clinical and Laboratory Standards Institute.[8] The following antimicrobials were tested: ceftazidime, chloramphenicol, levofloxacin, and trimethoprim/sulfamethoxazole.

Statistical analysis

Descriptive statistics was used for all the studied variables. Conformity of the data obtained in measurements to normal distribution was analyzed using the Kolmogorov–Smirnov

test. Data in conformity with normal distribution were analyzed using Student *t* test, and those not conforming to normal distribution were analyzed using the Mann–Whitney *U* test. Data obtained by measurement are given as mean ± standard deviation. Data obtained by counting are presented as numbers (%); analyses were done using the Chi-square test. Statically significant parameters were included to multivariate logistic regression model in univariate analyses. Results of the analysis are presented as *p* values, odds ratios (ORs), and 95% confidence intervals (CIs). A *p* value less than 0.05 was regarded as statistically significant.

Results

Stenotrophomonas maltophilia was isolated in 46 clinical samples between January 2003 and August 2008. It was isolated from tracheal aspiration in 41 (90%) samples, purulent ocular discharge in two (4%) samples, blood in two (4%) samples, and urine in one (2%) sample. Twenty-three samples (50%) were excluded because these patients had no infection criteria and these samples were accepted as colonization. A total of 23 samples from different patients were accepted to be associated with *S maltophilia* infections. The demographic characteristics of the patients with *S maltophilia* infection and the control group are shown in Table 1. Of the 23 patients with *S maltophilia* infections, 11 (48%) were females and 12 (52%) were males, with mean birth weight, gestational age, and postnatal age of 2,176 ± 928 g, 33.9 ± 4.5 weeks, and 6.4 ± 8.0 days, respectively. *Stenotrophomonas maltophilia* infections were more frequently observed in newborns with a birth weight less than 2,500 g and gestational age less than 37 weeks.

Two neonates (9%) had positive blood culture for *S maltophilia*. *Stenotrophomonas maltophilia* was isolated from purulent ocular discharge in two neonates (9%) and tracheal aspiration culture in 19 (82%) neonates. All neonates fulfilled the definitions of sepsis, conjunctivitis, and VAP. There was no polymicrobial infection in these 23 patients. The most active antimicrobial agents were trimethoprim/sulfamethoxazole (87%), levofloxacin (76%), and chloramphenicol (63%). Trimethoprim/sulfamethoxazole (TMP–SMZ) was used in 18 patients, levofloxacin was used in three patients, and ciprofloxacin eye drop was used in two neonates with conjunctivitis. Sixty-seven percent ($n = 30$) of the control patients had neonatal pneumonia, and the others had nosocomial sepsis caused by pathogens other than *S maltophilia*.

Invasive-procedure (including mechanical ventilation, intubation, and urinary catheter) exposure to aminoglycoside and carbapenem, TPN, H2 blockers, exposure to steroids, cholestasis, and duration of hospitalization were significantly associated with *S maltophilia* infections (Table 2). Durations of mechanical ventilation, urinary catheter, and TPN were statistically significantly longer in newborns associated with *S maltophilia* infections than in those in controls (Table 2). Four neonates with *S maltophilia* infections—one of them with sepsis and the others with VAP—died during the study period. The mortality rate for *S maltophilia* infections was 17%. The mortality rate was statistically significantly higher in newborns with *S maltophilia* infections than that in the controls ($p = 0.011$).

On multivariate analysis, invasive procedures (OR, 18.81; 95% CI, 1.9–184.6; $p = 0.012$) and duration of hospitalization (OR, 1.06; 95% CI, 1.004–1.133; $p = 0.037$) were determined to be the risk factors for *S maltophilia* infection (Table 3).

Discussion

This is the first study to investigate the predisposing factors and clinical characteristics of *S maltophilia* infections in the neonatal period. *Stenotrophomonas maltophilia* infections are an important cause of life-threatening nosocomial infections in children.[3] Because *S maltophilia* is resistant to empirical antibiotics (such as cefotaxime, ampicillin, gentamicin, etc.) used in neonatal infections. Increasing

Table 1 Characteristics of cases of *S maltophilia* and control group

Characteristic	*S maltophilia* ($n = 23$)	Control group ($n = 45$)	*p*
Birth weight (g)	2,176 ± 928	2,537 ± 823	0.124
≥2,500	10 (43)	27 (60)	0.195
≤2,499	13 (57)	18 (40)	0.255
Gestational age (wk)	33.9 ± 4.5	35.2 ± 3.7	0.058
≥37	8 (35)	26 (58)	0.072
$\leq 36^{6/7}$	15 (65)	19 (42)	
Delivery type			
Vaginal	9 (39)	27 (60)	0.128
Caesarean	14 (61)	18 (40)	
Sex			
Female	11 (48)	20 (44)	0.803
Male	12 (52)	25 (56)	
Postnatal age at hospitalization (d)	6.4 ± 8.0	4.7 ± 5.2	0.890
Prolonged rupture of membranes	1 (4)	4 (9)	0.656

Data are presented as *n* (%) or mean ± standard deviation.
$36^{6/7}$ = 36 weeks plus 6 days; *S maltophilia* = *Stenotrophomonas maltophilia*.

Table 2 Risk factors of *Stenotrophomonas maltophilia* infections

Characteristic	*S maltophilia* ($n = 23$)	Control group ($n = 45$)	p
Invasive procedures	21 (91)	13 (29)	0.001
Mechanical ventilation	21 (91)	6 (13)	0.001
Duration of mechanical ventilation (d)	13.5 ± 20.7	0.7 ± 1.8	0.001
Urinary catheter	12 (52)	4 (9)	0.001
Duration of urinary catheter (d)	4.1 ± 6.4	0.2 ± 0.7	0.001
Umbilical catheter	6 (26)	8 (18)	0.529
Duration of umbilical catheter (d)	1.2 ± 2.2	0.7 ± 2.0	0.409
Exposure to antimicrobial agent	23 (100)	27 (60)	0.001
Penicillin	7 (30)	26 (58)	0.060
Aminoglycoside	19 (83)	23 (51)	0.012
Cephalosporin	1 (4)	5 (11)	0.656
Carbapenem	18 (78)	14 (31)	0.001
TPN	20 (87)	12 (27)	0.001
Duration of TPN (d)	15.5 ± 20.9	4 ± 10.5	0.001
Histamine 2 blockers	21 (91)	10 (22)	0.001
Corticosteroid therapy	7 (30)	0 (0)	0.001
Cholestasis	6 (26)	1 (2)	0.005
Elevated liver enzymes	2 (9)	3 (7)	0.554
Low serum albumin level	6 (26)	9 (20)	0.792
Duration of hospitalization (d)	50.8 ± 44	10.8 ± 11.7	0.001

Data are presented as n (%) or mean $\pm$ standard deviation.
TPN = total parenteral nutrition.

monitoring of the premature infants, especially those with very low birth weights and prolonged hospitalization, has increased the observance of nosocomial *S maltophilia* infection rates in newborns. *Stenotrophomonas maltophilia* causes nosocomial pneumonia, bacteremia, central nervous system infections, endocarditis, and ophthalmological, urinary tract, bone and joint, skin and soft tissue, and gastrointestinal infections.[1,9] The respiratory tract is the most common site of *S maltophilia* infections.[10,11] In our study, 82% of the *S maltophilia*-related infections were VAP, 9% were sepsis, and 9% were conjunctivitis.

Differentiating colonization from infection is difficult, especially in cultures obtained from tracheal aspiration.[11] Only 19 of 41 (46%) tracheal aspiration samples were accepted as infected in our study. This finding is in accordance with literature. del Toro et al.[11] reported that 49% of the patients with positive respiratory samples were accepted to have a respiratory tract infection.

Various risk factors have been reported for infection or colonization by *S maltophilia*, including prior antibiotic therapy; prolonged hospitalization; presence of a central venous catheter, neutropenia, or cytotoxic chemotherapy; immunosuppressive therapy; prolonged stay in the intensive care unit; mechanical ventilation or tracheotomy; underlying disease (hepatobiliary, chronic pulmonary, and cardiovascular diseases; organ transplantation; dialysis; intravenous drug use; and infection with the human immunodeficiency virus or malignancy); corticosteroid therapy; exposure to patients with *S maltophilia* wound infection; received parenteral nutrition; and transportation to hospital by airplane.[1,5,11–13]

In our study, invasive-procedure (including mechanical ventilation, intubation, urinary catheter) exposure to aminoglycoside and carbapenem, TPN, H2 blockers, exposure to steroids, cholestasis, and duration of hospitalization were significantly associated with *S maltophilia* infections. Because the study group had a significantly lower gestational age and low birth weight, they had long-term hospitalization and more often had been exposed to invasive procedures. Nosocomial sepsis is common in these groups. Nosocomial sepsis further increases hospitalization time and exposure to invasive procedures. Previous exposure to broad-spectrum antimicrobial agents, especially carbapenem, ampicillin, gentamicin, vancomycin, metronidazole,

Table 3 Risk factors of *Stenotrophomonas maltophilia* infections (multivariate analysis)

Characteristic	Odds ratio	95% Confidence interval	p
Invasive procedures	18.81	1.9–184.6	0.012
Duration of hospitalization	1.06	1.004–1.133	0.037
Gestational age (wk)	1.19	0.890–1.605	0.235
Total parenteral nutrition	0.23	0.022–2.342	0.214
Cholestasis	1.58	0.069–36.121	0.773
Carbapenem	1.01	0.896–1.132	0.111

piperacillin, cefotaxime, ceftazidime, ciprofloxacin, tobramycin, and cefepime, is one of the significant risk factors for the development of *S maltophilia* colonization and infection.[14–17] Carbapenem and aminoglycosides are empirically used for nosocomial sepsis in our unit. In our study, 78% and 83% of the neonates with *S maltophilia* infection were exposed to carbapenem and aminoglycosides, respectively, before the onset of *S maltophilia* infection. These antibiotics may cause *S maltophilia* colonization in the respiratory tract. Moreover, *S maltophilia* constitutes 3% of hospital-acquired blood stream infections in our hospital.[18] These results indicate that *S maltophilia* is a common causative agent in nosocomial infection in our hospital.

Cholestasis was determined as a significant risk factor in the development of *S maltophilia* infection on univariate analysis and was not an independent risk factor on multivariable analysis; we considered that cholestasis was more related to prolonged hospitalization, parenteral nutrition, and exposure to invasive procedures, rather than being a direct predisposing factor for infection.

H2 blockers are frequently used in patients in the NICU to prevent the development of stress ulcers and bleeding. They raise intragastric pH, which may enhance the colonization of the stomach by gram-negative bacteria and thereby contribute to the development of nosocomial pneumonia.[19] Cook et al.[20] reported an increased risk of pneumonia associated with the use of H2-receptor antagonists. We determined a relationship between the use of H2-receptor antagonists and *S maltophilia* infection.

Management of *S maltophilia*-associated infection is difficult because many strains of *S maltophilia* display resistance to multiple antibiotics. It appears that TMP–SMZ; ticarcillin-clavulanate; and quinolones, such as levofloxacin or ciprofloxacin, are the most sensitive antibiotics for *S maltophilia*-associated infections.[3,5,12,21–24] The increasing resistance to TMP–SMZ represents an important problem for laboratory staff and clinicians.[25] Gales et al.[26] reported that the resistance to TMP–SMZ is increasing. The rate of resistance to TMP–SMZ ranges from 2% in Canada and Latin America to 10% in Europe. In a previous study in our hospital, the level of TMP–SMZ resistance was 2.3%,[22] and the rise to 13% in our study demonstrates this increasing resistance.

There is a concern over using TMP–SMZ in the neonatal period. TMP–SMZ competes with bilirubin for binding to albumin, and it can increase the level of indirect bilirubin. Hypoalbuminemia contributes to an increase in the level of indirect bilirubin. Hypoalbuminemia can be observed in the course of *S maltophilia* infections. Hypoalbuminemia and competition of TMP–SMZ with bilirubin for binding to albumin are a potential risk for hyperbilirubinemia. However, neonatal hyperbilirubinemia is commonly observed in the first week of life, and *S maltophilia* infections usually occur later than the first week. In our study, 23% of *S maltophilia* infections occurred in the first week of life, but no hyperbilirubinemia was observed. It has been reported that no adverse side effects, including increased indirect hyperbilirubinemia, associated with the use of TMP–SMZ, were observed in the neonatal period.[27] In our study, no other adverse side effects were observed to accompany TMP–SMZ. We, therefore, recommend TMP–SMZ for antimicrobial therapy of *S maltophilia* infection.

Lai et al.[21] reported that low serum albumin level can be used as a poor prognostic factor for *S maltophilia* bacteremia. However, we determined no statistically significant difference in serum albumin levels between cases with *S maltophilia* infection and the controls.

The mortality rates associated with *S maltophilia* infections ranged from 21% to 40.6% in adult and pediatric patients.[21,23,24,28] Delayed treatment for *S maltophilia* increases the mortality rate.[29] The mortality rate in our study (17%) was lower than that in the literature. Early detection and suitable antimicrobial therapy was effective in the improved outcome in our patients.

In conclusion, the most important risk factors for *S maltophilia* infection in neonates are invasive procedures; previous exposure to antibiotics, such as carbapenem and aminoglycoside; and prolonged hospitalization. Invasive procedure is a risk factor for nosocomial infections, such as *S maltophilia*, but invasive procedures are required critically ill neonates. For this reason, hand hygiene is the best method to prevent nosocomial infections. Broad-spectrum antibiotics should be avoided as much as possible in NICU patients, and agent/factor-specific antibacterial treatment should be administered. Patients being discharged as early as possible will also reduce infection frequency. We conclude that TMP–SMX is an appropriate choice for *S maltophilia* infection, and that this can be safely used in neonates. *Stenotrophomonas maltophilia* should be considered as a possible agent in neonates with high *Stenotrophomonas* infection risk factors. Early diagnosis and the commencement of appropriate antibiotics reduce mortality.

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