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ARTICLE

Stenotrophomonas maltophilia in the respiratory tract of medical intensive care unit patients

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Abstract The purpose of this study was to investigate characteristics of critically ill patients with *Stenotrophomonas maltophilia* (*S. maltophilia*) isolated from the respiratory tract, to identify risk factors for *S. maltophilia*-pneumonia and intensive care unit (ICU) mortality and to analyze antibiotic susceptibility of *S. maltophilia*. This was a retrospective analysis of 64 medical ICU patients with *S. maltophilia* in the respiratory tract. Thirty-six patients fulfilled the criteria for diagnosis of pneumonia. A significantly higher lung injury score (LIS) was observed in patients with pneumonia compared to patients with colonization (p=0.010). Independent risk factors for *S. maltophilia*-pneumonia were higher Sequential Organ Failure Assessment (SOFA) score (p=0.009) and immunosuppression (p=0.014). Patients with *S. maltophilia*-pneumonia had higher ICU mortality within a 28-day follow-up (p=0.040) and higher hospital mortality (p=0.018) than patients with colonization. The highest antibiotic susceptibility rates were observed to trimethoprim-sulfamethoxazole, tigecycline, and moxifloxacin. Higher SOFA score when *S. maltophilia* was isolated (p=0.001) and development of renal failure (p=0.021) were independent risk factors for ICU mortality. Higher SOFA score and immunosuppression are independent risk factors for *S. maltophilia*-pneumonia. Patients with *S. maltophilia*-pneumonia have a significantly higher ICU mortality within a 28-day follow-up, hospital mortality and LIS compared to patients with *S. maltophilia*-colonization.

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Introduction

Stenotrophomonas maltophilia (*S. maltophilia,* formerly called *Xanthomonas maltophilia* or *Pseudomonas maltophilia,* first identified in 1958) is a non-fermentative gram-negative bacillus (NF-GNB) [1]. In critically ill patients colonization and infection with NF-GNB are frequent and associated with poor outcomes [2, 3]. *S. maltophilia* has been recognized as an emerging nosocomial pathogen [4, 5]. Among a variety of different infection sites, the most frequent infections caused by this pathogen are pneumonia and bacteremia [5].

The therapy of *S. maltophilia* infections is challenging because this pathogen is characterized by resistance to many antibiotics. This extended antibiotic resistance to extended-spectrum penicillins, third-generation cephalosporins, carbapenems, and aminoglycosides is due to a number of antibiotic resistance determinants including reduced outer membrane permeability, beta-lactamases and enzymes inactivating aminoglycosides as well as multidrug efflux pumps [6–8]. The bacteriostatic drug trimethoprim-sulfamethoxazole has been the antibiotic of choice for this pathogen [4]. Variable susceptibility rates have been reported for the quinolone ciprofloxacin [5]. In vitro studies revealed promising results regarding susceptibility of *S. maltophilia* to moxifloxacin [4, 5, 9, 10].

In oncology patients, studies have characterized risk factors for *S. maltophilia* colonization, infections and bacteremia [11–15]. In patients with cystic fibrosis, *S. maltophilia* has been identified as an emerging pathogen for infections of the respiratory tract [16, 17]. It has been shown that infections related to *S. maltophilia* are more frequent in patients with neutropenia and immunosuppression as well as burn patients and organ transplant recipients [11, 14, 18–22]. The majority of studies on *S. maltophilia* infections investigated *S. maltophilia* bacteremia and catheter-associated *S. maltophilia* infections [23–26]. However, despite the increasing frequency of NF-GNB infections in intensive care unit (ICU) patients, the role of *S. maltophilia* colonization or infection of the respiratory tract in these patients is not well investigated [27, 28].

This retrospective study was conducted in critically ill medical ICU patients with *S. maltophilia* colonization or infection of the respiratory tract. The aim of the study was to investigate clinical characteristics in these patients and antibiotic susceptibility of *S. maltophilia* as well as to identify risk factors for *S. maltophilia* infection (pneumonia) and ICU mortality.

Materials and methods

Study design, setting, and patients

This retrospective study was conducted in three medical ICUs (25 beds) of a German university hospital. We analyzed the medical records of all patients admitted to the medical ICUs between November 2005 and December 2009. We identified 64 patients with *S. maltophilia* isolated from the respiratory tract (*S. maltophilia* isolated from microbiologic culture from bronchoalveolar lavage (BAL) or tracheal aspiration). The study was approved by the local ethics committee. Need for informed consent was waived for this retrospective analysis.

Definitions

For definition of pulmonary infection (i.e. pneumonia) associated with *S. maltophilia* we used modified criteria proposed by the US Centers for Disease Control and Prevention. *S. maltophilia*-associated pneumonia was diagnosed by a positive microbiologic culture from BAL or tracheal aspiration accompanied by radiographic signs of pulmonary infection (presence of new or increasing infiltrates on chest radiograph) and at least two of the following clinical criteria of pulmonary infection: abnormal temperature (>38.3°C or <35.0°C), abnormal leucocyte count (leucocyte count >10,000/μL or increase in leucocyte count >25% or leucocyte count <5,000/μL), or macroscopically purulent tracheal secretions. *S. maltophilia* colonization was defined as a positive microbiologic culture for *S. maltophilia* without the above-mentioned clinical signs for pulmonary infection/pneumonia.

Immunosuppression was defined as presence of neutropenia (neutrophil granulocytes <1,500/μL), medical immunosuppression or HIV infection.

To quantify the severity of pulmonary dysfunction, the lung injury score (LIS) was calculated as reported previously [29].

Microbiological testing

Antibiotic susceptibility testing of *S. maltophilia* isolates was performed according to Clinical and Laboratory Clinical Standards Institute standards, using a 0.5 McFarland inoculum on Mueller-Hinton plates. The following disk diffusion breakpoints (< = resistant; > = susceptible) were used: polymyxin B 300 μg 11/12 mm, ceftazidime 30 μg 14/18 mm, ciprofloxacin 5 μg 15/21 mm, moxifloxacin 5 μg 17/21 mm, trimethoprim-sulfamethoxazole 1.25/23.75 μg 10/16 mm, and tigecycline 15 μg 14/19 mm. Antibiotic susceptibility testing was not always performed for all antibiotic agents. Therefore, data on susceptibility to moxifloxacin and trimethoprim-sulfamethoxazole are missing in one patient each, data on susceptibility to polymyxin B are missing in three patients, and data on susceptibility to tigecycline are missing in 17 patients.

Statistical analysis

All statistical tests were conducted two-sided in an explorative manner on a 5% level of significance. Analyses were performed using PASW statistics, version 18.0 (SPSS Inc., Chicago, Illinois, USA). Due to violations of the normal distribution continuous variables were compared using the nonparametric Mann-Whitney-U test. Categorical variables were analyzed using the chi-squared test or Fisher's exact test when appropriate. Multivariate logistic regression analyses were performed to identify risk

factors for *S. maltophilia* pneumonia and ICU mortality. Variables considered to be a risk factor in advance or showing a p-value <0.100 in the univariate analysis were entered into the multivariate model. Stepwise forward variable selection was used to define the final independent risk factors. Adjusted odds-ratios and 95% confidence intervals are reported for logistic regression analyses. To identify independent risk factors for *S. maltophilia* pneumonia, the following factors were included in multivariate regression analysis: age, neutropenia, medical immunosuppression, immunosuppression (as defined in the methods section), COPD, nicotine abuse, development of renal insufficiency, presence of endotracheal tube, tracheostomy, ICU mortality, hospital mortality, Simplified Acute Physiology Score II (SAPS II score), Sequential Organ Failure Assessment (SOFA) score, leucocyte count on the day of *S. maltophilia* isolation, and duration of mechanical ventilation before *S. maltophilia* isolation. Factors included in the multivariate binary logistic regression analysis regarding risk factors associated with ICU mortality were *S. maltophilia*-related pneumonia, gender, admission from another hospital, liver cirrhosis as reason for ICU admission, liver failure on ICU admission, renal failure during ICU stay, liver failure during ICU stay, SAPS II score, SOFA score, presence of endotracheal tube, and need for mechanical ventilation when *S. maltophilia* was isolated.

Survival rates were estimated according to Kaplan-Meier curves and compared between groups by log-rank tests. Descriptive statistics for categorical factors are given by absolute and relative frequencies. Descriptive statistics for continuous factors are given by median, range and interquartile range (IQR) while the latter equals the span between the 25th and 75th percentile.

Results

Patients' characteristics

Sixty-four critically ill ICU patients with *S. maltophilia* isolated from the respiratory tract were enrolled in this study. Basic demographic data and patients' characteristics are stated in Table 1.

ICU treatment

The reasons for ICU admission and interventions during ICU treatment are shown in Table 2.

S. maltophilia-related colonization or infection

The median time between ICU admission and first isolation of *S. maltophilia* from the respiratory tract was 10.0 days (range, 0–55 days; IQR, 2.5–14.5 days) (Table 2). Before the first isolation of *S. maltophilia* patients had been treated in the hospital for a median time period of 15.0 days (range, 2–77 days; IQR, 8.0–25.5 days) without differences between the patients with *S. maltophilia* infection or colonization (median, 15.5 days; range, 2–77 days; IQR, 7.5–30.5 days compared to median, 14.5 days; range, 2–62 days; IQR, 10.5–24.0 days, respectively; p=0.823). At the time of first isolation of *S. maltophilia* from the respiratory tract, 36 patients (56%) fulfilled the criteria for the diagnosis of pulmonary infection/pneumonia, whereas the diagnosis of *S. maltophilia* colonization of the respiratory tract was made in 28 patients (44%). Serum levels of the laboratory infection parameter C-reactive protein (CRP) were significantly higher in patients with respiratory tract infection compared to patients with colonization of the respiratory tract (median, 13.1 mg/dL; range, 1.3–43.0 mg/dL; IQR, 5.6–20.4 mg/dL compared to median, 5.4 mg/dL; range, 0.8–29.6 mg/dL; IQR, 2.4–15.6 mg/dL, respectively; p=0.029).

Data regarding pulmonary function and mechanical ventilation

Data regarding respiratory function and mechanical ventilation are shown in Table 3. A significantly higher LIS at the time of first *S. maltophilia* isolation was observed in patients with *S. maltophilia*-related pneumonia compared to patients with *S. maltophilia* colonization.

Risk factors associated with S. maltophilia pneumonia

In univariate analysis, factors associated with *S. maltophilia* pneumonia (in contrast to *S. maltophilia* colonization of the respiratory tract) were: higher SOFA score on the day of first *S. maltophilia* isolation (p=0.002), immunosuppression (p=0.004), neutropenia (p=0.006), higher SAPS II score on the day of first *S. maltophilia* isolation (p=0.020) and higher serum CRP levels on the day of first *S. maltophilia* isolation (p=0.029) (Tables 1 and 3). In multivariate binary logistic regression analysis, higher SOFA score on the day of first *S. maltophilia* isolation (p=0.009; odds-ratio, 1.2; 95% confidence interval, 1.0–1.4) and immunosuppression (p=0.014; odds-ratio, 4.9; 95% confidence interval, 1.4–17.4) were identified as independent risk factors associated with *S. maltophilia* pneumonia.

Outcome of patients with S. maltophilia colonization and infection

Patient outcome is presented in Table 4. Kaplan-Meier analysis demonstrated a significantly higher ICU mortality within a follow-up of 28 days in patients with *S. maltophilia*-related pneumonia (p=0.040; Fig. 1). Patients

Table 1 Demographic data and patients' characteristics

Characteristics	All patients (n=64)	*S. maltophilia* colonization (n=28)	*S. maltophilia* infection (n=36)	p-value	ICU survivors (n=38)	ICU non-survivors (n=26)	p-value
Demographic data							
Gender, n (%)	42 male (66%), 22 female (34%)	20 male (71%), 8 female (29%)	22 male (61%), 14 female (39%)	p=0.389	29 male (76%), 9 female (24%)	13 male (50%), 13 female (50%)	p=0.029*
Age, years	66.0; 19–91; 57.5–72.0	68.5; 19–91; 58.0–76.0	64.0; 26–86; 57.5–68.5	p=0.088	67.5; 19–85; 56.0–72.0	64.0; 26–91; 58.0–75.0	p=0.732
Height, cm	170; 143–189; 165–180	173; 143–187; 165–180	170; 160–189; 165–180	p=0.450	172; 143–189; 165–180	170; 159–182; 165–180	p=0.704
Weight, kg	74.5; 45–145; 62.3–80.0	75.0; 51–145; 65.0–85.0	74.0; 45–110; 60.0–80.0	p=0.280	75.0; 50–145; 67.0–84.0	66.3; 45–110; 54.0–80.0	p=0.066
Scores							
APACHE II score	26.5; 9–46; 21.5–31.5	26.5; 9–42; 18.0–31.0	27.0; 13–46; 23.5–32.5	p=0.436	27.5; 9–37; 23.0–30.0	26.0; 12–46; 18.0–35.0	p=0.748
SAPS II score on ICU admission	55.5; 29–97; 45.5–69.5	54.0; 29–87; 44.5–67.0	56.0; 37–97; 49.0–72.0	p=0.258	53.5; 29–91; 45.0–68.0	56.0; 35–97; 48.0–79.0	p=0.473
SOFA score on ICU admission	11.0; 2–19; 7.0–13.0	10.0; 3–19; 6.5–12.0	11.5; 2–18; 7.5–13.5	p=0.110	10.0; 2–19; 7.0–12.0	11.0; 3–18; 9.0–13.0	p=0.343
SAPS II score (day of S. *maltophilia* isolation)	56.0; 27–106; 46.5–67.0	49.0; 28–85; 43.0–59.5	60.5; 27–106; 50.0–70.5	p=0.020*	49.0; 27–81; 41.0–59.0	63.0; 36–106; 56.0–80.0	p<0.001*
SOFA score (day of S. *maltophilia* isolation)	10.0; 1–21; 6.0–12.5	8.0; 1–19; 5.5–11.0	12.0; 1–21; 9.0–14.5	p=0.002*	8.0; 1–16; 5.0–11.0	12.5; 4–21; 11.0–17.0	p<0.001*
Pre-existing medical conditions							
Neutropenia, n (%)	12 (19%)	1 (4%)	11 (31%)	p=0.006*	5 (13%)	7 (27%)	p=0.202
Immunosuppression, n (%)	24 (38%)	5 (18%)	19 (53%)	p=0.004*	13 (34%)	11 (42%)	p=0.511
COPD, n (%)	18 (28%)	9 (32%)	9 (25%)	p=0.528	10 (26%)	8 (31%)	p=0.697
Diabetes mellitus, n (%)	13 (20%)	6 (21%)	7 (19%)	p=0.845	8 (21%)	5 (19%)	p=0.859
Nicotine abuse, n (%)	18 (28%)	11 (39%)	7 (19%)	p=0.080	13 (34%)	5 (19%)	p=0.191
Alcohol abuse, n (%)	14 (22%)	8 (29%)	6 (17%)	p=0.253	8 (21%)	6 (23%)	p=0.847
Malignancy, n (%)	27 (42%)	9 (32%)	18 (50%)	p=0.151	16 (42%)	11 (42%)	p=0.987

S. maltophilia Stenotrophomonas maltophilia, *ICU* intensive care unit, *APACHE II* score Acute Physiology and Chronic Health Evaluation II score, *SAPS II* score Simplified Acute Physiology Score II, *SOFA* score Sequential Organ Failure Assessment score

Where applicable data are presented as: median; range; interquartile range

p-values <0.05 are indicated with an asterisk

Table 2 Intensive care unit treatment

Description	All patients (n=64)	*S. maltophilia* colonization (n=28)	*S. maltophilia* infection (n=36)	p-value	ICU survivors (n=38)	ICU non-survivors (n=26)	p-value
Reason for ICU admission							
respiratory insufficiency, n (%)	25 (39%)	8 (29%)	17 (47%)	p=0.129	14 (37%)	11 (42%)	p=0.660
Cirrhosis of the liver, n (%)	12 (19%)	5 (18%)	7 (19%)	p=0.872	4 (11%)	8 (31%)	p=0.055
Cardiogenic shock, n (%)	8 (13%)	4 (14%)	4 (11%)	p=0.721	6 (16%)	2 (8%)	p=0.456
Sepsis, n (%)	6 (9%)	3 (11%)	3 (8%)	p=1.000	3 (8%)	3 (12%)	p=0.680
Pancreatitis, n (%)	3 (5%)	2 (7%)	1 (3%)	p=0.577	3 (8%)	0 (0%)	p=0.265
Gastrointestinal bleeding, n (%)	1 (2%)	0 (0%)	1 (3%)	p=1.000	0 (0%)	1 (4%)	p=0.406
Admission to ICU							
Transfer to ICU from normal ward, n (%)	37 (58%)	14 (50%)	23 (64%)	p=0.264	19 (50%)	18 (69%)	p=0.126
Transfer to ICU from another hospital, n (%)	13 (20%)	7 (25%)	6 (17%)	p=0.411	11 (29%)	2 (8%)	p=0.038*
Transfer to ICU from operating room, n (%)	3 (5%)	2 (7%)	1 (3%)	p=0.577	2 (5%)	1 (4%)	p=1.000
ICU stay							
Length of ICU stay, days	23.0; 2–123; 12.0–41.5	24.5; 3–74; 14.5–42.0	18.0; 2–123; 9.5–38.5	p=0.215	23.0; 2–77; 13.0–33.0	24.0; 3–123; 11.0–50.0	p=0.520
Length of ICU stay before *S. maltophilia*	10.0; 0–55; 2.5–14.5	11.0; 0–38; 6.5–14.0	8.0; 1–55; 2.0–16.5	p=0.266	9.0; 1–25; 3.0–13.0	11.0; 0–55; 2.0–22.0	p=0.362
Length of ICU stay after *S. maltophilia*	10.0; 0–80; 4.5–22.5	11.5; 0–63; 5.5–26.6	9.5; 0–80; 4.0–20.5	p=0.420	10.0; 0–70; 4.0–20.0	9.5; 0–80; 5.0–50.0	p=0.853
Organ failure on ICU admission							
Respiratory, n (%)	51 (80%)	22 (79%)	29 (81%)	p=0.845	31 (82%)	20 (77%)	p=0.649
Cardiac, n (%)	45 (70%)	17 (61%)	28 (78%)	p=0.138	26 (68%)	19 (73%)	p=0.689
Renal, n (%)	23 (36%)	10 (36%)	13 (36%)	p=0.974	13 (34%)	10 (38%)	p=0.728
Neurologic, n (%)	48 (75%)	20 (71%)	28 (78%)	p=0.561	29 (76%)	19 (73%)	p=0.769
Digestive, n (%)	4 (6%)	3 (11%)	1 (3%)	p=0.311	1 (3%)	3 (12%)	p=0.295
Hepatic, n (%)	27 (42%)	11 (39%)	16 (44%)	p=0.678	11 (29%)	16 (62%)	p=0.010*
During ICU hospitalization							
Tracheostomy, n (%)	13 (20%)	9 (32%)	4 (11%)	p=0.038*	10 (26%)	3 (12%)	p=0.149
Endotracheal tube, n (%)	42 (66%)	15 (54%)	27 (75%)	p=0.073	20 (53%)	22 (85%)	p=0.008*
Central venous catheter, n (%)	55 (86%)	24 (86%)	31 (86%)	p=1.000	31 (82%)	24 (92%)	p=0.291
Arterial catheter, n (%)	59 (92%)	25 (89%)	34 (94%)	p=0.646	33 (87%)	26 (100%)	p=0.074
Shaldon catheter for dialysis, n (%)	17 (27%)	7 (25%)	10 (28%)	p=0.803	8 (21%)	9 (35%)	p=0.228
Urinary catheter, n (%)	57 (89%)	24 (86%)	33 (92%)	p=0.689	34 (89%)	23 (88%)	p=1.000

S. maltophilia Stenotrophomonas maltophilia, *ICU* intensive care unit

Where applicable data are presented as: median; range; interquartile range

p-values <0.05 are indicated with an asterisk

with *S. maltophilia*-associated pneumonia had a significantly higher hospital mortality than patients with *S. maltophilia* colonization of the respiratory tract (p=0.018) (Table 4).

Risk factors for ICU mortality

In univariate analysis, ICU mortality was significantly associated with higher SAPS II score on the day of first *S. maltophilia* isolation (p<0.001), higher SOFA score on the day of first *S. maltophilia* isolation (p<0.001), development of renal failure during the ICU stay (p=0.006), need for mechanical ventilation on the day of first *S. maltophilia* isolation (p=0.007), cerebral/neurological dysfunction during the ICU stay (p=0.008), hepatic dysfunction on ICU admission (p=0.010), development of liver failure during the ICU stay (p=0.011), higher LIS on the day of first *S. maltophilia* isolation (p=0.012), lower pO2/FiO2 ratio on the day of first *S. maltophilia* isolation (p=0.025), and female gender (p=0.029) (Tables 1, 2 and 3). Multivariate

Table 3 Pulmonary function and mechanical ventilation

Description	All patients (n=64)	*S. maltophilia* colonization (n=28)	*S. maltophilia* infection (n=36)	p-value	ICU survivors (n=38)	ICU non-survivors (n=26)	p-value
Mechanical ventilation required, n (%)	51 (80%)	20 (71%)	31 (86%)	p=0.148	26 (68%)	25 (96%)	p=0.007*
Duration of mechanical ventilation, days	15.0; 0–115; 8.5–28.5	21.5; 0–73; 11.5–38.0	13.5; 0–115; 7.5–24.5	p=0.103	14.5; 0–74; 6.0–27.0	17.5; 2–115; 11.0–40.0	p=0.114
Duration of mechanical ventilation before diagnosis of *S. maltophilia*, days	7.0; 0–47; 2.0–11.5	9.5; 0–28; 3.0–12.0	3.5; 0–47; 1.5–11.0	p=0.094	6.5; 0–25; 2.0–11.0	9.0; 0–47; 2.0–12.0	p=0.380
Duration of mechanical ventilation after diagnosis of *S. maltophilia*, days	7.5; 0–84; 2.0–16.5	9.0; 0–63; 2.0–24.0	6.0; 0–84; 2.0–11.0	p=0.506	6.5; 0–67; 1.0–12.0	9.0; 0–84; 5.0–24.0	p=0.106
pO2/FiO2 (day of S. *maltophilia* isolation)	190.9; 43.7–376.4; 133.3–246.7	220.6; 85.7–376.4; 143.8–297.6	187.5; 43.7–366.7; 125.0–238.2	p=0.267	223.8; 93.7–366.7; 161.7–274.3	155.1; 43.7–376.4; 124.6–212.5	p=0.025*
LIS (day of S. *maltophilia* isolation), points	1.67; 0.00–3.00; 1.00–2.00	1.33; 0.00–2.33; 0.67–1.67	1.67; 0.33–3.00; 1.33–2.33	p=0.010*	1.33; 0.00–2.33; 1.00–1.67	2.00; 0.00–3.00; 1.33–2.33	p=0.012*

S. maltophilia, *Stenotrophomonas maltophilia*, *ICU* intensive care unit, *LIS* lung injury score

Where applicable data are presented as: median; range; interquartile range

p-values <0.05 are indicated with an asterisk

binary logistic regression analysis identified SOFA score on the day of first *S. maltophilia* isolation (p=0.001; odds-ratio, 1.4; 95% confidence interval, 1.1–1.6) and development of renal failure in the course of the ICU stay (p=0.021; odds-ratio, 4.8; 95% confidence interval, 1.3–18.4) as independent risk factors associated with ICU mortality.

Polymicrobial infections

In 33 (52%) of the 64 patients, other bacteria were isolated from the respiratory tract at the same time as *S. maltophilia* or within 7 days after the first isolation of *S. maltophilia*. The most frequently isolated co-pathogens were *Enterococcus* species (17 patients), *Coagulase-negative Staphylococcus* species (10 patients), *Escherichia coli* (7 patients), *Viridans group Streptococci* (6 patients), *Pseudomonas aeruginosa* (4 patients), *Enterobacter* cloacae (4 patients), *Klebsiella pneumoniae* (3 patients), *Staphylococcus aureus* (3 patients), *Enterococcus faecium* (3 patients) and *Serratia marcescens* (2 patients). Presence of a polymicrobial infection was significantly associated with hospital mortality (mortality 19/33 patients (58%) in patients with polymicrobial infection compared to 10/31 patients (32%) in patients without polymicrobial infection; p=0.042).

Antibiotic treatment

Fifty-eight (91%) of the 64 patients had been treated with at least one antibiotic agent before *S. maltophilia* was isolated from the respiratory tract. Thirty-seven patients (58%) had been exposed to carbapenems prior to first isolation of *S. maltophilia*. Extended-spectrum penicillins (piperacillin/sulbactam) had been used in 34 patients (53%). Macrolids had been administered in 32 patients (50%). Twenty-five patients (39%) had been treated with vancomycin, 11 (17%) with second and third generation cephalosporins and 11 (17%) with ciprofloxacin. Only two patients (3%) had been treated with moxifloxacin before the first isolation of *S. maltophilia* from the respiratory tract.

In patients exposed to carbapenems prior to isolation of *S. maltophilia* from the respiratory tract, *S. maltophilia*-related pneumonia was significantly more often diagnosed compared to patients without exposure to carbapenems (pneumonia in 25/37 patients (68%) in patients exposed to

Table 4 Intensive care unit and hospital mortality

Outcome	All patients (n=64)	*S. maltophilia* colonization (n=28)	*S. maltophilia* infection (n=36)	p-value
ICU mortality, n (%)	26 (41%)	8 (29%)	18 (50%)	p=0.083
Hospital mortality, n (%)	29 (45%)	8 (29%)	21 (58%)	p=0.018*

S. maltophilia Stenotrophomonas maltophilia, *ICU* intensive care unit

p-values <0.05 are indicated with an asterisk

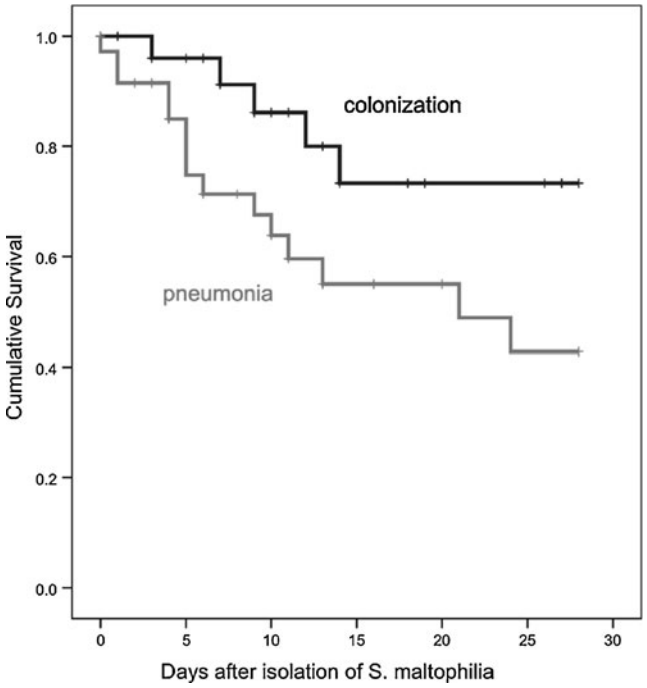

Fig. 1 Kaplan-Meier survival curve for patients with *Stenotrophomonas maltophilia* pneumonia and pulmonary colonization. Kaplan-Meier survival curve for patients with *Stenotrophomonas maltophilia* (*S. maltophilia*) pneumonia (*grey line*) and pulmonary colonization (*black line*); $p=0.040$

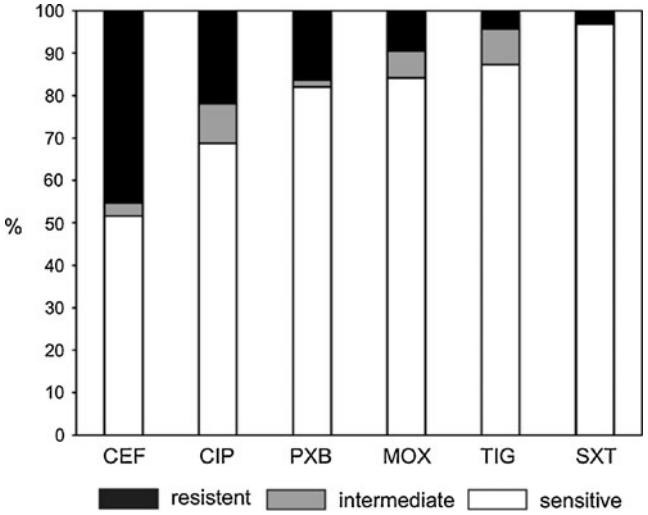

Fig. 2 Antibiotic susceptibility of *Stenotrophomonas maltophilia*. Antibiotic susceptibility of 64 *Stenotrophomonas maltophilia* isolates from the respiratory tract of 64 critically ill patients. Antibiotic susceptibility is depicted in % of isolates that were resistant, intermediate or sensitive to the antibiotic agent. Antibiotic agents: *CEF* ceftazidime, *CIP* ciprofloxacin, *PXB* polymyxin B, *MOX* moxifloxacin, *TIG* tigecycline, *SXT* trimethoprim-sulfamethoxazole

carbapenems compared to 11/27 patients (41%) in patients not exposed to carbapenems; $p=0.033$).

Antibiotic susceptibility

Antibiotic susceptibility is depicted in Fig. 2. In 84% of cases *S. maltophilia* was susceptible to moxifloxacin at the time of the first isolation of *S. maltophilia* from the respiratory tract. In 24 patients with *S. maltophilia* initially susceptible to moxifloxacin, *S. maltophilia* was isolated at least once more from the respiratory tract at a later time point. In 50% of cases *S. maltophilia* was then no longer susceptible to moxifloxacin.

The rate of antibiotic susceptibility to ciprofloxacin was significantly lower in patients treated with ciprofloxacin prior to first isolation of *S. maltophilia* (4/11 patients (36%)) compared to patients not treated with ciprofloxacin before *S. maltophilia* isolation (40/53 patients (75%)) ($p=0.027$).

Discussion

Sixty-four critically ill patients with *S. maltophilia* pneumonia or pulmonary colonization were included in this retrospective cohort study.

In the present study the patients' characteristics are different compared to previously presented studies that were conducted in interdisciplinary ICUs. The medical ICU patients included in our study showed higher SAPS II score, higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the duration of the ICU stay was longer compared to previous data [27, 28].

In multivariate binary logistic regression analysis, higher SOFA score on the day of first *S. maltophilia* isolation and immunosuppression were identified as independent risk factors for the development of *S. maltophilia* pneumonia. These findings are in accordance with previous data showing that immunosuppression and a debilitated clinical state are associated with *S. maltophilia* infections [5, 22].

Although the over-all ICU mortality rate was not significantly different between patients with *S. maltophilia* pneumonia or colonization, patients with pneumonia caused by *S. maltophilia* showed a significantly higher ICU mortality during a 28-day follow-up and higher in-hospital mortality. In accordance, in previous studies *S. maltophilia* infection has been shown to be associated with bad outcomes and high mortality rates [27, 30].

Mechanical ventilation was needed in 51 patients (80%) in our study. Although more patients with *S. maltophilia* pneumonia were mechanically ventilated in the present study compared to patients with colonization of the respiratory tract (86% vs. 71%), that difference did not reach statistic significance. However, in our study a significantly higher LIS score and significantly higher serum CRP levels at the time of first *S. maltophilia*

isolation were observed in patients with *S. maltophilia* pneumonia compared to patients with *S. maltophilia* colonization. The high proportion of patients requiring mechanical ventilation reflects the critical illness of the enrolled patients and is probably due to the fact that this study focused on patients with pulmonary *S. maltophilia* colonization and infection. However, the proportion of intubated and mechanically ventilated patients is comparable to that in the studies by Nseir et al. and Barchitta et al. both investigating *S. maltophilia*-associated infections in intensive care patients [27, 31]. As expected, in other studies characterizing both normal ward and ICU patients with *S. maltophilia* bacteremia the proportion of mechanically ventilated patients was markedly lower [24, 26, 32]. In our study the duration of mechanical ventilation before and after the isolation of *S. maltophilia* was not significantly different in patients with *S. maltophilia* pneumonia compared to patients with *S. maltophilia* colonization of the respiratory tract. In previous studies duration of mechanical ventilator support was revealed as a risk factor for the development of pneumonia and acquisition of *S. maltophilia* in general [28, 31].

In one-third of the patients in our study, bacterial co-pathogens were isolated from the respiratory tract when *S. maltophilia* colonization/infection was diagnosed. This frequency of polymicrobial infections is in accordance with previously reported data in patients with *S. maltophilia* pneumonia and *S. maltophilia* bacteremia [11, 24, 32, 33]. One study investigating the impact of positive *S. maltophilia* blood cultures in a tertiary care hospital in Singapore revealed markedly higher rates of polymicrobial bacteremia (77%) [34].

In accordance with previous data, the majority of patients (91%) in our study had been treated with at least one antibiotic prior to isolation of *S. maltophilia*. Several studies have demonstrated an association of exposure to broad-spectrum antibiotics with *S. maltophilia* infection [5, 26, 35]. In our study more patients (nearly 60%) had been treated with carbapenems before *S. maltophilia* was isolated compared to previous studies [26, 35]. The use of carbapenems has been previously shown to be associated with acquisition of *S. maltophilia* in several studies [35, 36]. In contrast, some studies did not identify exposure to carbapenems as a risk factor for *S. maltophilia* infection, whereas the use of broad-spectrum antimicrobial drugs other than carbapenems was associated with acquisition of *S. maltophilia* [11, 28, 37]. It has been hypothesized that exposure to broad-spectrum antimicrobial drugs in general might be more important than exposure to any single antibiotic [5]. In our study, *S. maltophilia* pneumonia was significantly more often diagnosed in patients who had been exposed to carbapenems compared to patients without exposure to carbapenems.

S. maltophilia usually shows antibiotic resistance to extended-spectrum penicillins, carbapenems, and aminoglycosides [6, 8]. In accordance with previous data, almost all *S. maltophilia* isolates in our study (97%) were susceptible to trimethoprim-sulfamethoxazole [26, 35, 38, 39]. However, there is evidence that the resistance rates to this drug are increasing [5, 40]. Besides trimethoprim-sulfamethoxazole, the most effective antibiotics against *S. maltophilia* in our study were the glycocycline antibiotic tigecycline, the quinolone moxifloxacin, and polymyxin B. Regarding treatment of *S. maltophilia* with ciprofloxacin, variable antibiotic susceptibility has been reported [5]. Only 69% of tested *S. maltophilia* isolates tested susceptible to the quinolone ciprofloxacin in our study. In accordance with previous data only about 50% of *S. maltophilia* isolates were susceptible to ceftazidime [5, 28].

This study was conducted retrospectively in a limited number of patients in three medical ICUs of a single university hospital in Germany. Therefore, the results and especially the data on antibiotic susceptibility of *S. maltophilia* may not apply for other hospitals and other geographic areas. Since molecular typing of *S. maltophilia* isolates is not performed in clinical routine we can not provide data on potential transmission of *S. maltophilia* isolates in our study. Moreover, our study is lacking a matched control group of patients without *S. maltophilia* colonization/infection.

In conclusion, the present study demonstrates that the severity of multiple organ dysfunction syndrome (reflected by a higher SOFA score) and immunosuppression are independent risk factors for *S. maltophilia* pneumonia in medical ICU patients with *S. maltophilia* isolated from the respiratory tract. *S. maltophilia* was previously considered to be a pathogen with limited pathogenicity. However, according to our data, patients with *S. maltophilia* pneumonia have a significantly higher ICU mortality within a follow-up of 28 days, hospital mortality and LIS compared to patients with *S. maltophilia* colonization. Regarding treatment of *S. maltophilia* infections, prospective controlled trials are needed to obtain in vivo data on the effectiveness of different antimicrobial agents.

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