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Original Research Article

Ventilator-Associated Pneumonia Caused by *Stenotrophomonas maltophilia* in ICU Patients: Clinical Characteristics, Antimicrobial Therapy, and Outcomes from a Multicenter Cohort

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Abstract: ***Background*:** Ventilator-associated pneumonia (VAP) is a common nosocomial infection in intensive care units, associated with high morbidity and mortality. *Stenotrophomonas maltophilia* has emerged as an opportunistic pathogen in critically ill patients, particularly following prolonged mechanical ventilation and prior antibiotic exposure. ***Methods*:** We conducted a retrospective multicenter study over a 4-year period in three intensive care units in France. Adult patients with VAP caused by *S. maltophilia* were included. Clinical, microbiological, and therapeutic data were collected. The primary outcome was 28-day mortality. ***Results*:** Among 293 VAP episodes caused by non-fermenting Gram-negative bacilli, 28 (9.55%) were due to *S. maltophilia*. Patients were elderly, highly comorbid, and severely ill, with a high rate of septic shock (71.1%). Polymicrobial infections were frequent (75%), mainly involving Enterobacterales. Empirical antibiotic therapy was active in only 14.3% of cases. Targeted therapy mainly relied on trimethoprim–sulfamethoxazole or levofloxacin. The 28-day mortality rate was 60.7%, with early deaths observed after diagnosis**.** ***Conclusion*:** *S. maltophilia* VAP occurs in high-risk ICU patients and is associated with frequent polymicrobial infections, inadequate empirical therapy, and high mortality, highlighting the need for improved management strategies.

Keywords: Ventilator-Associated Pneumonia – *S.Maltophilia* –ICU- Mortality.

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units and represents a major cause of morbidity and mortality among critically ill patients [1, 2].

Non-fermenting Gram-negative bacilli (NFGNB) play a major role in the epidemiology of these infections. Among them, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have historically been the most frequently implicated pathogens. However, other opportunistic organisms have emerged over the past decades, including *Stenotrophomonas maltophilia* [3–5].

The global epidemiology of VAP caused by NFGNB shows considerable regional variation. Higher incidences have been reported in several regions of Asia, Southern Europe, and Latin America, where high antibiotic pressure, prolonged mechanical ventilation, and the severity of underlying diseases promote the selection of these microorganisms [6].

In this context, *Stenotrophomonas maltophilia* has progressively been recognized as an emerging opportunistic pathogen among hospitalized ICU patients [4-8].

In Europe, several epidemiological studies have reported a gradual increase in nosocomial infections caused by *S. maltophilia*, particularly in intensive care units. In France, this pathogen is increasingly identified in respiratory infections among mechanically ventilated patients, likely due to prolonged exposure to broad-spectrum antibiotics, extended hospital stays, and the presence of significant comorbidities [9, 10].

VAP caused by *S. maltophilia* represents a particularly concerning clinical entity because of the high mortality associated with this infection, which has

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been reported to range from 30% to 50% in critically ill patients [9-11].

Several factors contribute to the severity of these infections. First, the clinical presentation is often difficult to distinguish from other forms of VAP caused by Gram-negative bacilli, which may delay diagnosis. Second, *S. maltophilia* exhibits intrinsic resistance to multiple classes of antibiotics commonly used in empirical treatment of severe infections, including most β-lactams, carbapenems, and aminoglycosides.

Consequently, empirical antibiotic regimens administered to patients with VAP are frequently inactive against this pathogen, which may delay the initiation of appropriate antimicrobial therapy and contribute to increased mortality [9-12].

Despite the growing importance of this microorganism in ICU respiratory infections, data regarding the clinical characteristics, therapeutic management, and outcomes of VAP caused by *S. maltophilia* remain limited, particularly in European and French cohorts [9, 10].

The objective of this study was to describe the clinical, microbiological, and therapeutic characteristics, as well as the outcomes, of patients with ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia* in a multicenter cohort of ICU patients in France.

METHODS

Study Design and Setting

We conducted a retrospective multicenter observational study over a 4-year period in three intensive care units belonging to the same hospital group in France. All episodes of ventilator-associated pneumonia (VAP) caused by non-fermenting Gram-negative bacilli were screened. The objective was to describe the clinical characteristics, microbiology, antimicrobial management, and outcomes of VAP caused by *Stenotrophomonas maltophilia*.

Study Population

Adult patients (≥18 years) admitted to the participating ICUs and diagnosed with VAP due to *S. maltophilia* were included.

VAP was defined according to international guidelines as pneumonia occurring ≥48 hours after initiation of invasive mechanical ventilation, associated with new or progressive pulmonary infiltrates and at least two of the following: fever or hypothermia, leukocytosis or leukopenia, or purulent respiratory secretions. Microbiological confirmation was based on quantitative cultures of endotracheal aspirates or bronchoalveolar lavage. *S. maltophilia* isolates were included when considered clinically significant by the treating physicians.

Data Collection

Clinical, microbiological, therapeutic, and outcome data were extracted from electronic medical records.

Collected Variables

- **Demographics and baseline characteristics:** age, sex, BMI, Charlson comorbidity index.
- **Severity of illness:** SAPS II at ICU admission, presence of septic shock at VAP diagnosis.
- **Infection-related variables:** early vs. late-onset VAP, number of VAP episodes, mono- or polymicrobial infection, associated microorganisms.
- **Antimicrobial therapy:** empirical treatment, appropriateness against *S. maltophilia*, targeted therapy, treatment duration, and de-escalation.
- **Outcomes:** clinical evolution, relapse, superinfection, duration of mechanical ventilation, ICU length of stay, and 28-day mortality.

Microbiological Analysis

Respiratory samples were processed according to standard procedures in the participating laboratories. Identification of isolates was performed using MALDI-TOF mass spectrometry. Quantitative cultures were interpreted using established thresholds, with bacterial loads $>10^7$ CFU/mL considered suggestive of active infection. Antimicrobial susceptibility testing followed EUCAST recommendations.

Definitions

- **Active Empirical Therapy:** at least one antibiotic with in vitro activity against *S. maltophilia* administered before microbiological results.
- **Polymicrobial Infection:** isolation of ≥1 additional microorganism in respiratory cultures at VAP diagnosis.
- **Relapse:** recurrence of *S. maltophilia* infection after initial improvement.
- **Superinfection:** new infection caused by another pathogen during ICU stay. The primary outcome was 28-day mortality after VAP diagnosis.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Categorical variables were presented as counts and percentages. Comparisons between 28-day survivors and non-survivors used the Student's t-test for continuous variables and Fisher's exact test for categorical variables. Relative risks (RR) with 95% confidence intervals were calculated to identify factors associated with mortality. A p-value <0.05 was considered statistically significant. Analyses were performed using standard statistical software.

RESULTS

Study Population

During the 4-year study period across the three hospitals of our hospital group, 293 episodes of ventilator-associated pneumonia (VAP) caused by non-fermenting Gram-negative bacilli were identified. Among these, 28 episodes (9.55%) were attributable to *Stenotrophomonas maltophilia* and were included in the present analysis.

The mean age of patients was 70 ± 10 years, and 64% were male. Most patients were hospitalized in the Jossigny intensive care unit (68%). All diagnoses were established from respiratory microbiological samples.

The mean body mass index was 28.35 (median 30). The mean Charlson Comorbidity Index was 5.4 (median 5), indicating a highly comorbid population. The mean Simplified Acute Physiology Score II (SAPS II) was 52.1 (median 49).

Septic shock was present in 20 patients (71.1%). Late-onset VAP accounted for 19 cases (67.9%), whereas 9 cases (32.1%) were classified as early-onset.

Notably, all patients had been exposed to systemic antibiotic therapy prior to the onset of *Stenotrophomonas maltophilia* ventilator-associated pneumonia.

Regarding the occurrence of VAP episodes, *S. maltophilia* infection occurred during the first episode in 7 patients, the second episode in 16 patients, the third episode in 4 patients, and the fourth episode in 1 patient.

Microbiological Findings

Respiratory cultures were polymicrobial in 21 cases (75%) and monomicrobial in 7 cases (25%).

The microorganisms most frequently associated with *S. maltophilia* belonged to the Enterobacterales family, representing the predominant group of co-isolated pathogens. Identified species included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus mirabilis*, and *Hafnia alvei*.

Other microorganisms included *Pseudomonas aeruginosa* and Gram-positive cocci such as *Staphylococcus aureus*.

Antimicrobial susceptibility testing of *S. maltophilia* isolates showed susceptibility rates of 100% to levofloxacin, 93% to trimethoprim–sulfamethoxazole, 61% to ticarcillin–clavulanate, and 29% to ceftazidime.

Antibiotic Therapy

Empirical antibiotic therapy most frequently included piperacillin–tazobactam (50%), followed by cefotaxime (28.5%), meropenem (10.7%), cefepime (7.1%), and imipenem (3.6%).

Empirical treatment consisted of monotherapy in 16 patients (57.1%) and combination therapy in 12 patients (42.9%), mainly including amikacin (41.7%), metronidazole (25%), or spiramycin (33.3%).

The mean duration of empirical therapy was 5.03 days, and it was active against *S. maltophilia* in only 4 cases (14.3%).

Targeted therapy consisted mainly of trimethoprim–sulfamethoxazole (67.9%), levofloxacin (21.4%), and ceftazidime (7.1%).

Targeted therapy was administered as monotherapy in 25 patients (89.3%) and combination therapy in 3 patients (10.7%), with a mean duration of 5.28 days. De-escalation was performed in 3 cases (10.7%).

Clinical Outcomes

Clinical improvement was observed in 39.3% of patients.

The 28-day mortality rate was 60.7% (17/28).

The mean duration of mechanical ventilation was 16 days, and the mean ICU length of stay was 21 days.

Relapse occurred in 10.7% of cases, and superinfection in 67.9%. Most infections occurred during the second episode of ventilator-associated pneumonia.

Kaplan–Meier Analysis

Kaplan–Meier survival analysis showed a progressive decline in survival following the diagnosis of ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*. Early mortality occurred within the first days after diagnosis, followed by a more gradual decrease in survival over time. The overall 28-day mortality rate was 60.7% (17/28)

Predictors of 28-Day Mortality

In the exploratory analysis of factors associated with 28-day mortality, none of the evaluated variables reached statistical significance. However, some trends were observed. Polymicrobial infection (RR 1.53) and multiple VAP episodes (RR 1.46) tended to be associated with increased mortality. Similarly, a higher Charlson comorbidity index (>4) was associated with a trend toward higher mortality (RR 1.27). Conversely, late-onset VAP and prolonged ICU stay appeared to be associated with a lower risk of death, although these associations were not statistically significant. The lack of statistical significance likely reflects the limited sample size of the cohort.

Key Highlights

- *Stenotrophomonas maltophilia* accounted for 9.55% of VAP caused by non-fermenting Gram-negative bacilli in our cohort.
- Polymicrobial infections were frequent (75%), with Enterobacterales as the predominant associated pathogens.
- Empirical antibiotic therapy was rarely active against *S. maltophilia* (14.3%), reflecting the intrinsic resistance profile of this organism.
- Trimethoprim–sulfamethoxazole and levofloxacin showed the highest susceptibility rates.
- Mortality remained high (60.7%), highlighting the severity of these infections in critically ill patients.

Conclusion

In this multicenter cohort of ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*, infections frequently occurred in severely ill and highly comorbid ICU patients, often during subsequent episodes of VAP. Polymicrobial infections were common, and empirical antibiotic therapy was infrequently active against this pathogen. Despite targeted therapy, clinical outcomes remained poor with a high 28-day mortality rate, emphasizing the clinical burden of *S. maltophilia* in ventilated patients.

Table 1: Baseline characteristics of patients with ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*

Characteristic	Value
Age, mean ± SD (years)	70 ± 10
Male sex, n (%)	18 (64%)
ICU of hospitalization – Jossigny, n (%)	19 (68%)
Respiratory samples, n (%)	28 (100%)
Body mass index, mean	28.35
Body mass index, median	30
Charlson Comorbidity Index, mean	5.4
Charlson Comorbidity Index, median	5
SAPS II score, mean	52.1
SAPS II score, median	49
Septic shock, n (%)	20 (71.1%)
Early-onset VAP, n (%)	9 (32.1%)
Late-onset VAP, n (%)	19 (67.9%)

Table 2: Antimicrobial susceptibility of *Stenotrophomonas maltophilia*

Antibiotic	Sensitive (n)	Resistant (n)	Susceptibility (%)
Ticarcillin–clavulanate	17	11	61%
Ceftazidime	8	20	29%
Levofloxacin	28	0	100%
Trimethoprim–sulfamethoxazole	26	2	93%

Table 3: Antibiotic therapy and outcomes

Empirical antibiotic therapy		**n**	**%**
	Antibiotic	14	50%
	Piperacillin–tazobactam Cefotaxime	8	28.5%
	Meropenem	3	10.7%
	Cefepime	2	7.1%
	Imipenem	1	3.6%
Empirical therapy characteristics	Monotherapy	16	57.1%
	Combination therapy	12	42.9%
	Mean duration of empirical therapy	5.03 days	14.3%
	Empirical therapy active against *S. maltophilia*	4	
Associated empirical antibiotics (n = 12)	Amikacin	5	41,7%
	Metronidazole	3	25%
	Spiramycin	4	33,3%
Targeted antibiotic therapy	Trimethoprim–sulfamethoxazole	19	67,9%
	Levofloxacin	6	21,4%
	Ceftazidime	2	7,1%
Targeted therapy characteristics	Monotherapy	25	89,3%
	Combination therapy	3	10,7%
	Mean duration	5,28	

Table 4: Predictors of 28-day mortality

	Vivants	Décédé	RR	P
Sex				
M	8	10	1,25	0,69
F	3	7		
BMI				
<25	3	7	1,20	0,71
>25	8	10		
Charlson index				
<4	6	7	1,27	0,65
>4	5	10		
SAPS II				
<58	6	13	0,37	0,12
>58	5	4		
Septic chock				
Yes	9	11	0,92	0,90
No	4	4		
VAP				
Early-onset	2	7	0,64	0,28
Late-onset	9	10		
Infection				
Monomicrobial	3	4	1,53	0,32
Polymicrobial	8	13		
Prolonged mechanical ventilation				
Yes	8	10	1,19	0,72
No	3	7		
Extended stay in intensive care				
Yes	8	8	0,75	0,46
No	3	9		
Relapse				
Yes	2	1	0,73	0,61
No	9	16		
Superinfection				
Yes	9	10	1,22	0,64
No	2	7		
number of PAVMs				
<1	3	4	1,46	0,41
>1	8	13		

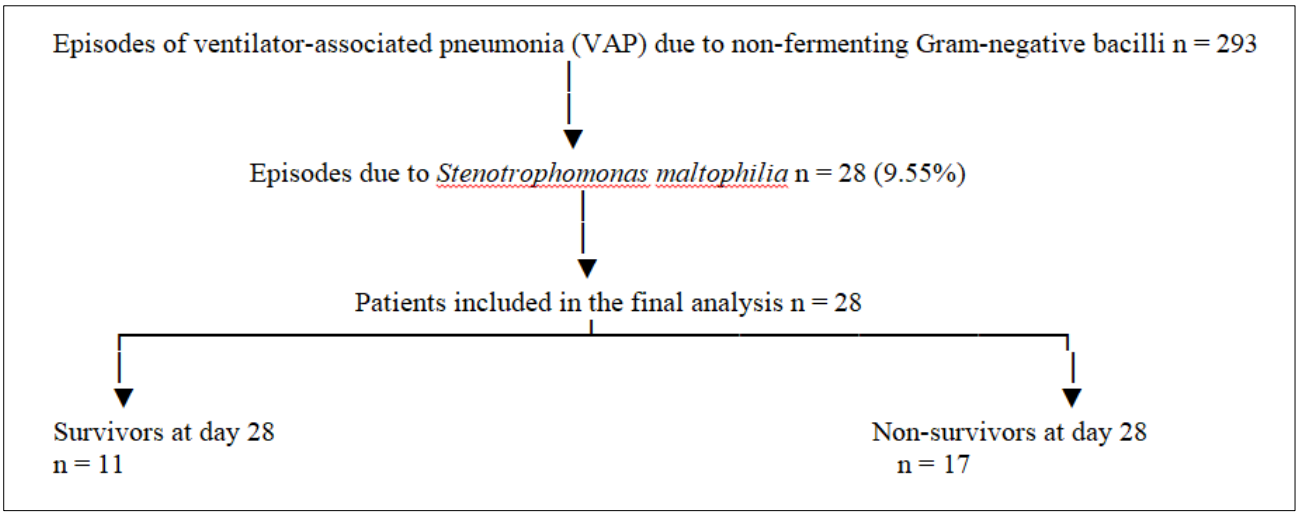

Figure 1: Study flowchart

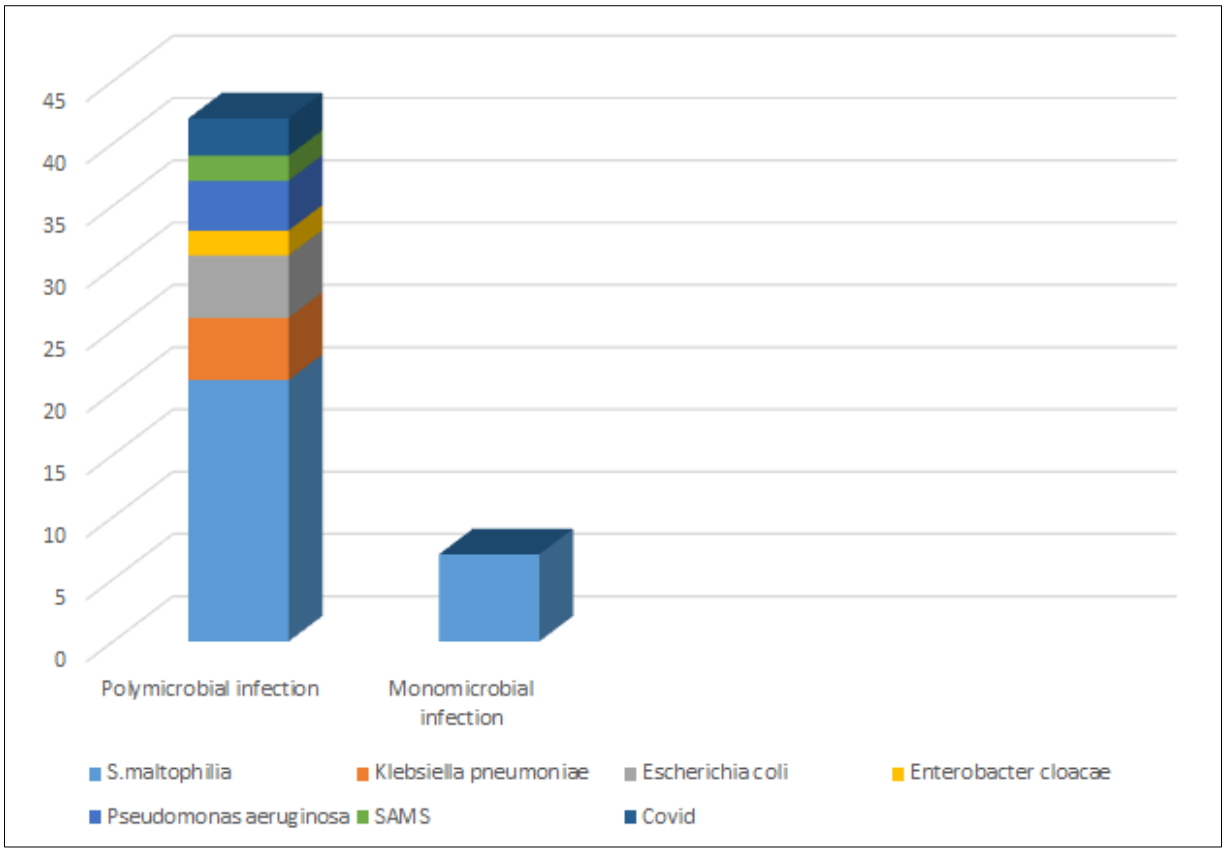

Figure 2: Microbiological pattern

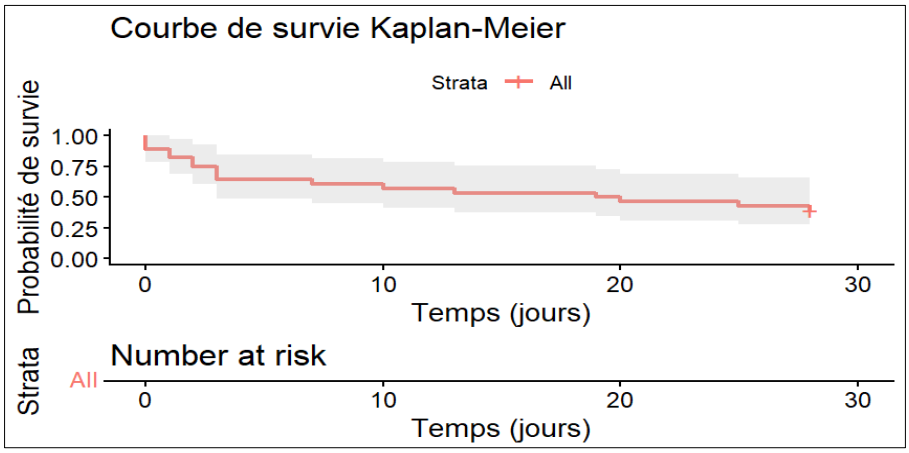

Figure 3: Kaplan–Meier survival curve for 28-day mortality in patients with ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*

DISCUSSION

Ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia* represents a challenging clinical condition in critically ill patients. This opportunistic pathogen is typically associated with prolonged ICU stay, prior exposure to broad-spectrum antibiotics, and substantial mortality. In our multicenter cohort, *S. maltophilia* accounted for 9.55% of ventilator-associated pneumonia caused by non-fermenting Gram-negative bacilli, confirming its increasing role among nosocomial respiratory pathogens in the intensive care setting.

Patients included in our study were characterized by advanced age, multiple comorbidities, and high severity of illness, as reflected by elevated SAPS II scores and the high prevalence of septic shock. These findings are consistent with previously published ICU cohorts describing *S. maltophilia* infections in patients with significant physiological impairment and high severity scores at diagnosis [9-13].

A notable observation in our cohort was that all patients had received antibiotic therapy prior to the onset of VAP, supporting the hypothesis that antibiotic pressure plays a key role in the emergence of this

pathogen. Previous investigations have consistently demonstrated that exposure to broad-spectrum antibiotics—particularly carbapenems and antipseudomonal β-lactams—is a major risk factor for *S. maltophilia* infections in critically ill patients [14, 15].

In our study, polymicrobial infection was observed in 75% of cases, highlighting the fact that *S. maltophilia* VAP frequently occurs as part of complex respiratory infections involving multiple pathogens. This observation is consistent with recent ICU studies reporting a high prevalence of polymicrobial pneumonia in patients infected with this organism [9-12]. The presence of multiple pathogens may complicate antimicrobial management and reflects the profound alteration of respiratory microbiota commonly observed during prolonged mechanical ventilation.

The interpretation of respiratory cultures may sometimes be challenging in ventilated patients because opportunistic organisms may represent colonization rather than true infection. In our cohort, however, the bacterial load in respiratory samples was greater than 10^7 CFU/mL, which strongly supports the diagnosis of true infection rather than simple colonization. Quantitative cultures above established thresholds are commonly used to improve the specificity of ventilator-associated pneumonia diagnosis in mechanically ventilated patients. Nevertheless, distinguishing infection from colonization remains challenging in critically ill patients because *Stenotrophomonas maltophilia* is known to colonize the respiratory tract, particularly after prolonged mechanical ventilation and prior antibiotic exposure.

Another important finding of our study is the low rate of active empirical antibiotic therapy, with only 14% of initial regimens being effective against *S. maltophilia*. This result is consistent with previous reports showing that empirical regimens commonly used in severe pneumonia frequently lack activity against this organism because of its intrinsic resistance to several antibiotic classes, including most β-lactams and carbapenems [15]. These findings underline the importance of early microbiological identification and prompt adaptation of antimicrobial therapy.

Antimicrobial susceptibility testing in our cohort confirmed high in vitro activity of trimethoprim–sulfamethoxazole and fluoroquinolones, particularly levofloxacin. These agents remain the cornerstone of therapy for *S. maltophilia* infections. Recent studies have demonstrated that appropriate antimicrobial therapy, especially regimens based on trimethoprim–sulfamethoxazole, is associated with improved outcomes in patients with severe *S. maltophilia* infections [9-12].

The 28-day mortality rate of 60.7% observed in our cohort is relatively high but remains within the range reported in previous studies conducted in critically ill populations. Recent reports have described ICU mortality rates ranging from approximately 39% to 50%, reflecting the severe underlying conditions and the complexity of infections in this patient population [14, 15].

Another noteworthy observation is that most infections occurred during a second episode of ventilator-associated pneumonia, suggesting that *S. maltophilia* may emerge during prolonged ICU stays under selective antibiotic pressure. This phenomenon has been previously described and is thought to reflect progressive ecological changes in the respiratory microbiota during extended mechanical ventilation and repeated antibiotic exposure.

The Kaplan–Meier survival analysis performed in our cohort showed a marked decline in survival during the first days following the diagnosis of ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*, followed by a more gradual decrease over time. This pattern suggests that a substantial proportion of deaths occurred early after infection onset, which likely reflects the high severity of illness in this population. Indeed, most patients in our cohort presented with significant comorbidities, high severity scores at ICU admission, and a high prevalence of septic shock at the time of VAP diagnosis.

Early mortality following ICU-acquired infections has been previously described in critically ill populations and is often associated with severe underlying disease and delayed initiation of appropriate antimicrobial therapy [12-15]. In the context of *S. maltophilia* infections, the intrinsic resistance of this organism to many commonly used empirical antibiotics frequently results in initial antimicrobial regimens that lack activity against the pathogen [15], which may contribute to worse outcomes during the early phase of infection.

The overall 28-day mortality observed in our study (60.7%) appears higher than that reported in several previous studies, where mortality rates generally range between 39% and 50% in critically ill patients with *S. maltophilia* infections [9-14]. Differences in patient characteristics, severity of illness, and ICU case mix may partly explain these variations.

Previous investigations have also suggested that mortality associated with *S. maltophilia* infections is often driven more by the severity of the underlying condition and host factors than by the pathogen itself [12-14]. In this regard, the early decline in survival observed in our Kaplan–Meier analysis likely reflects the combined impact of severe critical illness, complex polymicrobial infections, and the challenges associated with early appropriate antimicrobial therapy in this setting.

In the exploratory analysis of prognostic factors, none of the evaluated variables reached statistical significance as predictors of 28-day mortality, likely due to the limited sample size of our cohort. Nevertheless, several trends were observed. Polymicrobial infection and multiple episodes of VAP appeared to be associated with a higher risk of mortality, while a higher Charlson comorbidity index also tended to be associated with worse outcomes. These observations are consistent with previous studies identifying comorbidity burden and infection complexity as important determinants of prognosis in *S. maltophilia* infections [12-14].

Conversely, late-onset VAP and prolonged ICU stay appeared to be associated with a lower risk of mortality in our cohort. These findings should be interpreted cautiously and may reflect a survivorship bias, whereby patients who survive the early phase of critical illness are more likely to develop late complications or prolonged hospitalizations.

Overall, our results suggest that mortality in patients with *S. maltophilia* VAP is multifactorial, resulting from the interaction between host characteristics, severity of illness, and infection complexity rather than from a single independent determinant. Larger multicenter studies are therefore needed to better identify prognostic factors and to optimize therapeutic strategies for this increasingly recognized pathogen in the ICU.

Strengths and Limitations

This study has several strengths. First, it was conducted in a multicenter ICU setting, which improves the generalizability of the findings and provides a broader representation of the epidemiology of *Stenotrophomonas maltophilia* ventilator-associated pneumonia. Second, detailed clinical, microbiological, and therapeutic data were collected for all patients, allowing a comprehensive characterization of the infection, antimicrobial management, and clinical outcomes. Third, the study specifically focused on VAP caused by *S. maltophilia*, an emerging pathogen that remains relatively understudied in ICU cohorts.

However, several limitations should be acknowledged. First, the retrospective design may have introduced information bias and limited the control of potential confounding factors. Second, the relatively small sample size reduces the statistical power of the study and may explain the absence of statistically significant predictors of mortality. Third, the study was conducted within hospitals belonging to the same hospital group, which may limit the external generalizability of the results. Finally, multivariate analysis could not be performed because of the limited number of cases.

Despite these limitations, our study provides valuable clinical and microbiological data regarding ventilator-associated pneumonia caused by *S. maltophilia* in critically ill patients and contributes to the growing literature on this emerging ICU pathogen.

Clinical Implications

These findings highlight the importance of considering Stenotrophomonas maltophilia as a potential pathogen in patients with ventilator-associated pneumonia who have prolonged ICU stay and prior exposure to broad-spectrum antibiotics. Early microbiological identification and prompt initiation of appropriate antimicrobial therapy may be essential to improve clinical outcomes in this high-risk population.

CONCLUSION

Ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia* occurred predominantly in severely ill and highly comorbid ICU patients in our multicenter cohort. These infections were frequently polymicrobial and were often preceded by exposure to broad-spectrum antibiotics, which may contribute to the emergence of this intrinsically resistant pathogen. Empirical antimicrobial therapy was rarely active against *S. maltophilia*, reflecting the therapeutic challenges associated with its resistance profile. Despite targeted antimicrobial treatment, clinical outcomes remained poor, with a high 28-day mortality rate. These findings highlight the need for increased awareness of *S. maltophilia* as a potential cause of VAP in mechanically ventilated patients and underscore the importance of early microbiological diagnosis and appropriate antimicrobial therapy. Larger multicenter studies are needed to better characterize prognostic factors and optimize management strategies for this increasingly recognized pathogen in the ICU.

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