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Keywords: ICU, mortality, Risk factors, VAP, GNB, SM

Abstract

Background: *Stenotrophomonas maltophilia* (*SM*) is increasingly identified in intensive care unit (ICU). This study aim to identify risk factors for *SM* ventilator-associated pneumonia (VAP) and whether it affects ICU mortality

Methods: Two nested matched case-control studies were performed based in OUTCOMEREA database. The first episodes of *SM*-VAP patients were matched with two different control groups: VAP due to other micro-organisms (VAP-other) and *Pseudomonas aeruginosa* VAP (Pyo-VAP). Matching criteria were the hospital, the SAPS II, and the previous duration of mechanical ventilation (MV).

Results: Of the 102 *SM*-VAP patients (6.2% of all VAP patients), 92 were matched with 375 controls for the *SM*-VAP/ other-VAP matching and 84 with 237 controls for the *SM*-VAP / *Pyo*-VAP matching. *SM*-VAP risk factors were an exposition to ureido/carboxypenicillin or carbapenem during the week before VAP, and respiratory and coagulation components of SOFA score upper to 2 before VAP. *SM*-VAP received early adequate therapy in 70 cases (68.6%). Risk factors for Day-30 were age (OR=1.03; p <.01) and Chronic heart failure (OR=3.15; p<.01). Adequate treatment, either monotherapy or combination of antimicrobials, did not modify mortality. There was no difference in 30-day mortality, but 60-day mortality was higher in patients with *SM*-VAP compared to Other-VAP (P=0.056).

Conclusions: In a large series, independent risk factors for the *SM*-VAP were ureido/carboxypenicillin or carbapenem exposure the week before VAP, and respiratory and coagulation components of the SOFA score > 2 before VAP. Mortality risk factors of SM-VAP were age and chronic heart failure. Adequate treatment did not improve *SM*-VAP prognosis.

INTRODUCTION

Stenotrophomonas maltophilia (*SM*) is a non-fermentative gram-negative bacteria involved in Intensive Care Unit (ICU) acquired infections(1, 2), including bloodstream infections, ventilator-associated pneumonia (VAP), skin and soft tissues infections, and rarely urinary tract infections. This ubiquitous bacteria found in water and soil forms biofilms that can enhance its ability to colonize medical devices and lower respiratory tract(2-4). *SM* is naturally highly resistant to most common antibiotics, such as broad-spectrum penicillin including carbapenems, cefepime, or piperacillin-tazobactam, and aminoglycosides. The drug of choice to treat *SM* infections is trimethoprim/sulfamethoxazole (TMX), although strains resistant to TMX are emerging (5, 6). Acquired resistance is also possible through integrons, plasmids, and transposons (3, 4, 7). *SM-VAP* usually ~~occurred~~ occurs after a prolonged duration of mechanical ventilation(3). Although *SM-VAP* represents no more than 6% of all VAP (8, 9), itis associated with high mortality rates, up to 77%(3, 10). A better knowledge of risk factors of *SM*-VAP may allow preventive strategies and adequate early antimicrobial therapy to improve the prognosis.

This study aimed to assess the characteristics of *SM*-VAP in a prospectively collected multicenter medical and surgical ICU setting, to identify risk factors for *SM*-VAP, and to evaluate the outcome of patients.

METHODS AND PATIENTS

We conduct a matched case-control study, based on prospectively collected multicenter French database OUTCOMEREA™ (11). All patients aged over 18 years admitted from 1997 to 2015 presenting at least one episode of VAP were included. Their clinical and biologic data were registered in the database each day of their ICU stay. The French Advisory

Committee approved this database collection for Data Processing in Health Research (CCTIRS) and the French Informatics and Liberty Commission (CNIL). The study was approved by the institutional review board of Clermont-Ferrand University, France.

Definition of pneumonia and Antimicrobial Treatment

The diagnosis of VAP was suspected in patients who had received at least 48 hours of mechanical ventilation (MV) and developed a new or persistent infiltrate on chest radiography that was associated with one of the following criteria: (1) purulent tracheal secretions, (2) fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, and (3) leukocytosis greater than 10 ^{9}G/L or leukopenia less than 4.10^{8} G/L. The diagnosis of VAP was confirmed by positive quantitative culture of a respiratory sample collected via bronchoalveolar lavage fluid (significant threshold, $\geq 10^4$cfu/ml) or plugged telescopic catheter (significant threshold, $\geq 10^3$cfu/ml) or protected specimen brush significant threshold, $\geq 10^3$cfu/ml) or quantitative endotracheal aspirate (significant threshold, $\geq 10^5$ cfu/ml). *SM-VAP* was diagnosed when *SM* was recovered at a significant concentration according to the type of sample.

Treatment was considered adequate when one antimicrobial for which the strain was susceptible *in vitro* was used in the first 24 hours after drawing the bronchial sample. The dose of the antimicrobials was not recorded. Three treatment groups were defined: (1) no adequate treatment within 24 hours defined as untreated *SM*-VAP group; and patients treated adequately within the first 24 hours were split in (2) only one active drug: monotherapy group and (3) more than one active drug: combination therapy group.

Data Collection

All relevant data from the medical records including clinical, laboratory, radiology, microbiology information and antibiotic were collected at admission and during the ICU stay (12). Patients were followed until day 60.

Statistical analyses

Characteristics of patients were described as count (percent) or median (interquartile range) for qualitative and quantitative variables, respectively, and were compared between patients' groups using chi-square or Mann-Whitney tests, as appropriate.

We designed two matched cohort analyses: (1) Patients with the first episode of *SM*-VAP were matched (1:n) with patients with VAP due to any other pathogen (other-VAP); (2) Patients with a first episode of *SM*-VAP were matched (1:n) with patients with *Pseudomonas aeruginosa* VAP (*Pyo*-VAP). The following criteria were used for both matching processes: same ICU, predicted hospital mortality assessed by SAPS II (± 10%), time interval between ICU admission and VAP onset, taking into account the time of VAP occurrence (±1 days if VAP occurs in the 7 first days, ±2 days between the 8^{th} and the 14^{th} days, ±3 days between the 15^{th} and 21^{st} days, ±4 days between the 22^{nd} and the 30^{th} days, ±5 days between the 31^{st} and the 45^{th} days, ±6 days between the 46th and the 60^{th} days, ±7 days between the 61^{st} and the 75^{th} ,±8 days between the 76^{th} and the 90^{th} days). We were able to match 92 cases with 375 controls for the *SM*-VAP/ other-VAP matching and 84 cases with 237 controls for the *SM*-VAP / *Pyo*-VAP matching. We computed the standardized mean differences for each variable to assess the quality of matching.

To identify the risk factors of *SM*-VAP occurrence, matched data were analyzed using conditional logistic regression with stepwise selection. Hematological failure was defined as the hematological component of the SOFA score > 2 on the two days before VAP occurrence.

To identify risk factors of death after *SM*-VAP occurrence, we used survival Cox models. Time zero (T0) was the *SM*-VAP occurrence. Variables identified as significantly associated with mortality by the univariate models were inserted into a multivariate model. To capture the severity of the underlying illness without overadjusting on the severity related to the VAP process we used prognostic factors measured 2 days before VAP. A subgroup analysis excluding co-infected *SM*-VAP was also planned. Survival plots were computed. The impact of adequate therapy using monotherapy and combination therapy was tested in the final model values less than 0.05 were considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

RESULTS

Epidemiology and clinical features

Among the 1,594 patients with VAP, 102 had at least one episode of *SM*-VAP (***Figure 1).*** *SM*-VAP onset occurred later after ICU admission compared to other-VAP and *Pyo*-VAP (12 [7- 17] days; 10 [6- 15] days and 9 [5- 14] days, respectively). Main characteristics of *SM*-VAP are in ***(Table 1)***. SM-VAP occurred more frequently in female, with a history of neutropenia, admitted for septic shock and more often associated with hematological organ failure. Compared to VAP due to other pathogens, *SM*-VAP was associated with significantly higher hospital mortality, and longer ICU stay (32.5 [20- 46] days versus 24 [15- 38] days, respectively ~~**(Table 1))**~~**.**

Risk factors of *SM*-VAP

Of the 102 episodes of *SM*-VAP, 92 were successfully matched to 375 patients with VAP due to other pathogens. The quality of the matching procedure was good (***supplemental Figure 1)***. Characteristics of *SM*-VAP and matched controls are on ***Supplemental Table 1***.

The univariate analysis showed that *SM*-VAP remained more frequent in female patients with hematological organ failure and shock. It was associated with an increased previous exposure to antimicrobial therapy and parenteral nutrition. On multivariate analysis, patients with SM-VAP were more frequently female, with a higher SOFA score. Uses of carbapenems and piperacillin-tazobactam within the previous week before VAP were also more frequent (**Table 2)**. Similarly, 84 episodes of SM VAP were matched to 234 episodes of Pyo VAP. Risk factors of SM VAP were also female gender, respiratory and haematological component of SOFA score and previous exposure to carbapnems of Piperacillin/tazobactam. (***Supplemental Table 2***). Previous use of cephalosprins, fluoroquinolones, aminoglycosides, macrolides were not different between groups.

Adequacy of antimicrobial therapy

SM-VAP was treated adequately in 70 cases (68.6%). The details of the number of patients treated with adequate monotherapy and combination therapy after *SM*-VAP diagnosis is on ***Supplemental Figure* 2 and *Supplemental Table 3*.** During the first day, 21/84 received adequate therapy (adequate monotherapy in 16 cases and dual active antibiotic therapy in 5 cases). SM was more frequently susceptible to Colistin (91.2%), Levofloxacin (94.4%), Cotrimoxazole (96.6%), ticarcillin-clavulanate (78.7%) than to other antimicrobials tested (Tigecyclin (43.5%); Ceftazidime (51.8%), Cefepime (30.3%)). ***Supplemental Table 4.***

Mortality of patients with SM-VAP

As compared to the matched other-VAP control group, the mortality rate was higher among patients with *SM*-VAP. But the mortality rate of the *SM*-VAP group was comparable to the mortality of the matched *Pyo*-VAP group (***Figure* 2**). Considering only the *SM*-VAP group, 42 patients (41.2%) died within 30 days after VAP onset. Age and chronic cardiac failures were the only variables associated with *SM*-VAP 30-day mortality (1.02[1.002-1.047] and 2.45[1.12-5.34], respectively **(Table3**))**.** Adequate therapy was not associated with improvement of prognosis (p=0.42 logrank test) regardless of the co-infection (***Supplemental Figure 3***).

DISCUSSION

A total of 102 patients with *SM*-VAP were analysed. To the best of our knowledge, this is the largest cohort of medical and surgical ICU patients with *SM*-VAP ever published.

We found that factors independently associated with *SM*-VAP occurrence were respiratory and coagulation components of the SOFA score > 2 before VAP, and exposure to imipenem and carboxy- or ureido-penicillin within the week before VAP. ICU stay was longer in patients with *SM*-VAP than in patients with VAP due to other pathogens. Risk factors associated with death in *SM*-VAP patients were age and chronic heart failure. Finally, compared to patients with *Pyo*-VAP, patients with *SM*-VAP were more frequently admitted to ICU with neutropenia, had higher median SOFA score at admission, and their first VAP occurred later on. There was no statistical difference in ICU- and hospital length of stay between *Pyo*-VAP and *SM*-VAP and no difference in mortality either.

SM-VAP is a rare pathology considered as an opportunistic pathogen, responsible for late-onset infections in patients with immunosuppression, or undergoing invasive procedures and long-lasting hospitalization(2, 3, 17, 18, 20). Our prevalence (6.4%)as well as the characteristics of the population are similar to those listed in the literature(2, 13, 14, 18, 19).~~*SM*-VAP is a relatively rare occurrence, accounting for 6.4% of all VAP in our study, in line with previous studies (2, 8, 13-17). Patient's characteristics were consistent with other studies of *SM*-VAP(2, 13, 14, 18, 19). The sex-ratio was in favor of male patients in SM-VAP, although the rate of male patients was lower than that in VAP due to other pathogens. Indeed, patients were mainly middle-aged males presenting severe diseases with a median SAPS II of 52. *SM* VAP occurred in patients with previous long duration of ICU stay and of mechanical ventilation, as compared to other VAP (2, 14). considered as an opportunistic pathogen, responsible for late-onset infections in patients with immunosuppression, or undergoing invasive procedures and long-lasting hospitalization(2, 3, 17, 18, 20). *SM* is generally. Immunosuppression has been described as a significant risk factor for *SM* bacteremia but to our knowledge, not explicitly associated with *SM*-VAP(3, 20).~~

Importantly, *SM*-VAP is associated with long exposure to broad-spectrum antimicrobials, as reflected in the univariate analysis of our study by the role of the duration of exposure to antibiotics within the week before the first *SM*-VAP, the median number of antibiotics used at the time of the first *SM*-VAP, and the exposure to broad-spectrum antibiotics such as ciprofloxacin, piperacillin-tazobactam or carbapenems within the week before VAP, in line with previous results (2, 14, 21). Indeed, in a prospective case-control study with 30 *SM* infections including 22 VAP, prior exposure to extended-spectrum cephalosporin was associated with *SM* infection in univariate analysis (2). In another study, only cefepime exposure was significantly associated with *SM*-VAP, but these results could be explained by a large prescription of cefepime in this survey (14). ICU procedures such as catheters, parenteral nutrition, sedation, dialysis, and catecholamine use have also been associated with the risk of *SM*-VAP in the literature (17). Contrarily to previous studies on *SM*

bloodstream infections (1, 22), the presence of a central venous catheter and parental nutrition was not associated with *SM*-VAP. It may indeed be explained by differences in pathophysiology of VAP and bloodstream infections, and also because our analysis was matched on patients' severity and ICU length of stay prior to VAP onset. ~~The need for tracheostomy was a significant risk factor for *SM*-VAP in a population of trauma patients, which was not confirmed in our general ICU patient population (14). This may be the result of more severe lung injury in trauma patients with pulmonary contusions which were not observed in our study~~. Multivariate analysis showed that respiratory failure (PaO2/FiO2 ratio below 300 mmHg) and hematological component of the SOFA score (platelet count below 100G/L) just before VAP onset were strongly associated with the risk of *SM*-VAP.

The crude mortality of *SM*-VAP was higher than the one observed in patients with other VAP, reflecting the fact the disease occurred later in the ICU stay (19, 23). After matching on previous duration of ICU stay, there was no difference in ICU- and day-30 mortality in the two case-control analyses. However, the day-60 mortality was higher in patients with *SM*-VAP compared to other-VAP, but not when compared to Pyo-VAP mortality.

To our knowledge, only one study, on a reduced cohort of six *SM*-VAP patients, assessed day-60 mortality. Mortality rate between *SM*-VAP and other-VAP were not different, which suggests that morbidity and mortality of patients with *SM*-VAP are similar to that of patients with VAP caused by other nosocomial Gram-negative bacilli(13).

Inadequate initial antimicrobial therapy is common for *SM* infections, as this bacteria is naturally resistant to most antibiotics used for the treatment of late-onset nosocomial infections, including carbapenem, piperacillin-tazobactam, and aminoglycosides (18).

Moreover, EUCAST (European Committee on Antimicrobial Susceptibility Testing) has provided antimicrobial susceptibility testing breakpoints for only one antibiotic that is trimethoprim-sulfamethoxazole(24). Other antibiotics inconsistently efficient in *SM* infections are ticarcillin-tazobactam, levofloxacin, ciprofloxacin, moxifloxacin, tigecycline, colistin, and ceftazidime (25, 26). Nevertheless, *in vitro* susceptibility rate was high for cotrimoxazole, levofloxacin and colistin with respectively 97%, 94% and 91% of susceptible strains, whereas susceptibility for ticarcillin-clavulanate was only 79%. Overall, 37% patients had an inadequate empirical treatment. While this rate sounds high, it is lower than the one observed in most of the previous studies (1, 2, 14, 18, 27).

We did not find any impact of the adequacy of treatment on *SM*-VAP outcome. Whether the adequacy of the initial therapy has an impact on the outcome in severe late-onset ICU-acquired infections is unclear. In the study of Tseng *et al*., inadequate initial antibiotic therapy was associated with an increased mortality of nosocomial pneumonia due to *SM* (OR=2.17), especially in case of polymicrobial infections(19). On the opposite, recent studies have shown the lack of impact of inadequate initial therapy on patients' outcome in various settings, including bloodstream infections due to *Enterobacteriaceae* and carbapenem-resistant gram-negative bacteria, or *Pseudomonas aeruginosa* VAP (18, 28-30).

Numerous factors could explain this counter-intuitive observation. First, *SM* was not the only recovered pathogen in 31% of the episodes and might be considered as a low pathogen in such VAPs. The coinfection with *P. aeruginosa* and *S. maltophilia* have been reported to impact negatively the prognosis (30). In our study, the treatment of the other pathogens was always adequate and co-infection was not associated with a poorer prognosis. Attributable mortality of *SM*-VAP is still unclear, but the presence of *SM* in the

lungs seems to have a deleterious effect on outcome in ICU patients. Second, patients with no clinical signs of severity could have had delayed treatment without any impact on the outcome. Third, treatment regimen, especially doses, could be inadequate in ICU patients with high distribution volumes.

Our study has several strengths. It is the biggest database of medical and surgical patients with *SM*-VAP. We used a high-quality database, with bacteriologically confirmed pneumonia and an audit of all bacteriological results before analyses. We took into account in our matching process the delay before VAP occurrence. For most patients, we recorded long-term follow-up data, making unlikely any bias due to informative censor. We computed the standardized mean differences for each variable to assess the quality of matching. This study has also some limitations. First, the analysis was retrospective, which allows for multiple biases. Second, 31% of *SM*-VAP were polymicrobial; this could have flaw risk factors identification and outcome; however, other studies had a similar approach (14, 31). Third, antibiotic taken before ICU admission were not monitored neither assessed as potential risk factors.

CONCLUSION

In this multicentre retrospective analysis of prospectively collected data from 102 patients with *SM*-VAP, exposure to carbapenem and carboxy- or ureido-penicillin during the week before VAP and the severity of disease with respiratory and hematological failures were independent risk factors for the *SM*-VAP occurrence. Strikingly, the prognosis of patients with *SM*-VAP was not modified by the adequacy of antimicrobial therapy. The prognosis of patients with *SM*-VAP was quite similar to the one of matched other-VAP or

291 *Pyo*-VAP when adjusted on severity at ICU admission and duration of ICU stay before VAP
292 onset.

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296 **List of abbreviations:**

297 **VAP**: Ventilator–acquired pneumonia

298 **ICU**: intensive care unit

299 ***SM*-VAP**: *Stenotrophomonas maltophilia* ventilator–acquired pneumonia

300 **Others- VAP**: Others microorganisms ventilator–acquired pneumonia

301 ***Pyo*-VAP:** *Pseudomonas aeruginosa* ventilator–acquired pneumonia

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Bibliography

1. Fihman V, Le Monnier A, Corvec S, et al. Stenotrophomonas maltophilia--the most worrisome threat among unusual non-fermentative gram-negative bacilli from hospitalized patients: a prospective multicenter study. J Infect 2012;64(4):391-398.
2. Nseir S, Di Pompeo C, Brisson H, et al. Intensive care unit-acquired Stenotrophomonas maltophilia: incidence, risk factors, and outcome. Crit Care 2006;10(5).
3. Looney WJ, Narita M, Muhlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. Lancet Infect Dis 2009;9(5):312-323.
4. Trifonova A, Strateva T. Stenotrophomonas maltophilia - a low-grade pathogen with numerous virulence factors. Infect Dis 2018;13:1-11.
5. Nicodemo AC, Paez JI. Antimicrobial therapy for Stenotrophomonas maltophilia infections. Eur J Clin Microbiol Infect Dis 2007;26(4):229-237.
6. Wang YL, Scipione MR, Dubrovskaya Y, et al. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of Stenotrophomonas maltophilia infections. Antimicrob Agents Chemother 2014;58(1):176-182.
7. Brooke JS. New strategies against Stenotrophomonas maltophilia: a serious worldwide intrinsically drug-resistant opportunistic pathogen: Expert Rev Anti Infect Ther. 2014 Jan;12(1):1-4. doi: 10.1586/14787210.2014.864553. Epub 2013 Dec 4.
8. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.
9. Soubirou JF, Gault N, Alfaiate T, et al. Ventilator-associated pneumonia due to carbapenem-resistant Gram-negative bacilli in an intensive care unit without carbapenemase-producing Enterobacteriaceae or epidemic Acinetobacter baumannii. Scand J Infect Dis 2014;46(3):215-220.
10. Paez JI, Tengan FM, Barone AA, et al. Factors associated with mortality in patients with bloodstream infection and pneumonia due to Stenotrophomonas maltophilia. Eur J Clin Microbiol Infect Dis 2008;27(10):901-906.
11. Ibn Saied W, Mourvillier B, Cohen Y, et al. A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia. Critical care medicine 2018.
12. Ibn Saied W, Souweine B, Garrouste-Orgeas M, et al. Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early- and late-onset VAP: An analysis of the OUTCOMEREA network. PloS one 2017;12(11):e0187791.

13. Scholte JB, Zhou TL, Bergmans DC, et al. Stenotrophomonas maltophilia ventilator-associated pneumonia. A retrospective matched case-control study. Infect Dis 2016;48(10):738-743.
14. Hanes SD, Demirkan K, Tolley E, et al. Risk factors for late-onset nosocomial pneumonia caused by Stenotrophomonas maltophilia in critically ill trauma patients. Clin Infect Dis 2002;35(3):228-235.
15. Guyot A, Turton JF, Garner D. Outbreak of Stenotrophomonas maltophilia on an intensive care unit. J Hosp Infect 2013;85(4):303-307.
16. Sader HS, Farrell DJ, Flamm RK, et al. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents 2014;43(4):328-334.
17. Chang YT, Lin CY, Chen YH, et al. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 2015;6(893).
18. Samonis G, Karageorgopoulos DE, Maraki S, et al. Stenotrophomonas maltophilia infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PloS one 2012;7(5):18.
19. Tseng CC, Fang WF, Huang KT, et al. Risk factors for mortality in patients with nosocomial Stenotrophomonas maltophilia pneumonia. Infect Control Hosp Epidemiol 2009;30(12):1193-1202.
20. Senol E, DesJardin J, Stark PC, et al. Attributable mortality of Stenotrophomonas maltophilia bacteremia. Clin Infect Dis 2002;34(12):1653-1656.
21. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157(2):531-539.
22. Boktour M, Hanna H, Ansari S, et al. Central venous catheter and Stenotrophomonas maltophilia bacteremia in cancer patients. Cancer 2006;106(9):1967-1973.
23. Falagas ME, Kastoris AC, Vouloumanou EK, et al. Attributable mortality of Stenotrophomonas maltophilia infections: a systematic review of the literature. Future Microbiol 2009;4(9):1103-1109.
24. Leclercq R, Canton R, Brown DF, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 2013;19(2):141-160.
25. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of Stenotrophomonas maltophilia isolates tested against tigecycline and agents commonly used for S. maltophilia infections. Antimicrob Agents Chemother 2010;54(6):2735-2737.
26. Metan G, Uzun O. Impact of initial antimicrobial therapy in patients with bloodstream infections caused by Stenotrophomonas maltophilia: Antimicrob Agents Chemother. 2005 Sep;49(9):3980-1. doi: 10.1128/AAC.49.9.3980-3981.2005.

27. Czosnowski QA, Wood GC, Magnotti LJ, et al. Clinical and microbiologic outcomes in trauma patients treated for Stenotrophomonas maltophilia ventilator-associated pneumonia. Pharmacotherapy 2011;31(4):338-345.
28. Zak-Doron Y, Dishon Benattar Y, Pfeffer I, et al. The Association between Empirical Antibiotic Treatment and Mortality in Severe Infections Caused by Carbapenem-Resistant Gram-Negative Bacteria: A Prospective Study. Clin Infect Dis 2018;27(4987600).
29. Sommer H, Timsit JF, von Cube M, et al. The Impact of Early Adequate Treatment on Extubation and Discharge Alive of Patients With Pseudomonas aeruginosa-Related Ventilator-Associated Pneumonia. Critical care medicine 2018;46(10):1643-1648.
30. Yin C, Yang W, Meng J, et al. Co-infection of Pseudomonas aeruginosa and Stenotrophomonas maltophilia in hospitalised pneumonia patients has a synergic and significant impact on clinical outcomes. Eur J Clin Microbiol Infect Dis 2017;36(11):2231-2235.
31. Nseir S, Deplanque X, Di Pompeo C, et al. Risk factors for relapse of ventilator-associated pneumonia related to nonfermenting Gram negative bacilli: a case-control study. J Infect 2008;56(5):319-325.

Figure legends

Figure 1: Population Flowchart

Figure 2: Mortality D-60 in the different VAP groups

Table 1: Baseline characteristics of the different VAP categories

Table 2: Risk factors for *Stenotrophomonas maltophilia* VAP

Table 3: Risk factors of 30-day and 60-day mortality in *Stenotrophomonas maltophilia* VAP

Appendix

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Supplemental material

E1: Univariate analyses for risk factors of *Stenotrophomonas maltophilia* ventilator-associated pneumonia as compared to their matched other-pathogens ventilator-associated pneumonia

E2: Univariate analyses for risk factors of *Stenotrophomonas maltophilia* ventilator-associated pneumonia as compared to their matched *Pseudomonas aeruginosa* ventilator-associated pneumonia

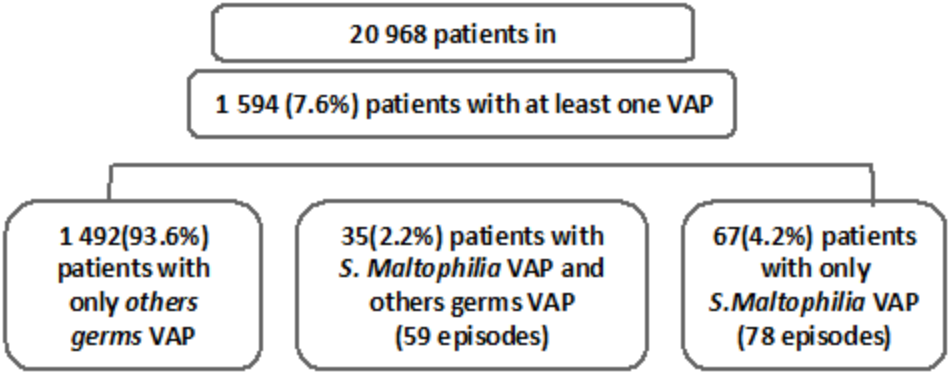
E3: Antibiotic adequacy and different antibiotic day of take in monotherapy or combination therapy

E4: Antimicrobial susceptibility testing for *Stenotrophomonas maltophilia* ventilator-associated pneumonia adequately treated

Supplemental *Figure 1*: Matching assessment for *Stenotrophomonas maltophilia* ventilator-associated pneumonia, other pathogens- ventilator-associated pneumonia and *Pseudomonas aeruginosa* ventilator-associated pneumonia

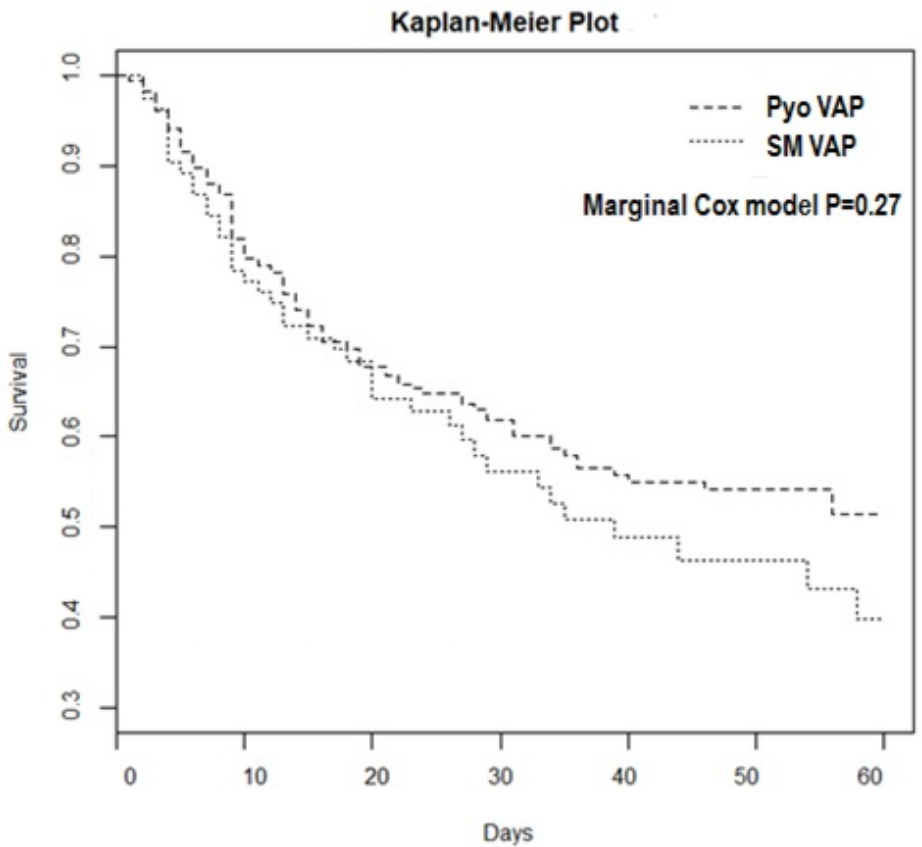
Supplemental Figure 2: *Antibiotic group and death occurrence in Stenotrophomonas maltophilia* ventilator-associated pneumonia

Supplemental Figure 3: *Comparing Day-30 mortality in Stenotrophomonas maltophilia ventilator-associated pneumonia without co-infection (65 episodes) and all Stenotrophomonas maltophilia ventilator-associated pneumonia (102 episodes) according to the treatment group*



[1] 102 episodes of *Stenotrophomonas maltophilia* ventilator acquired pneumonia (VAP)

Figure 1: population Flowchart



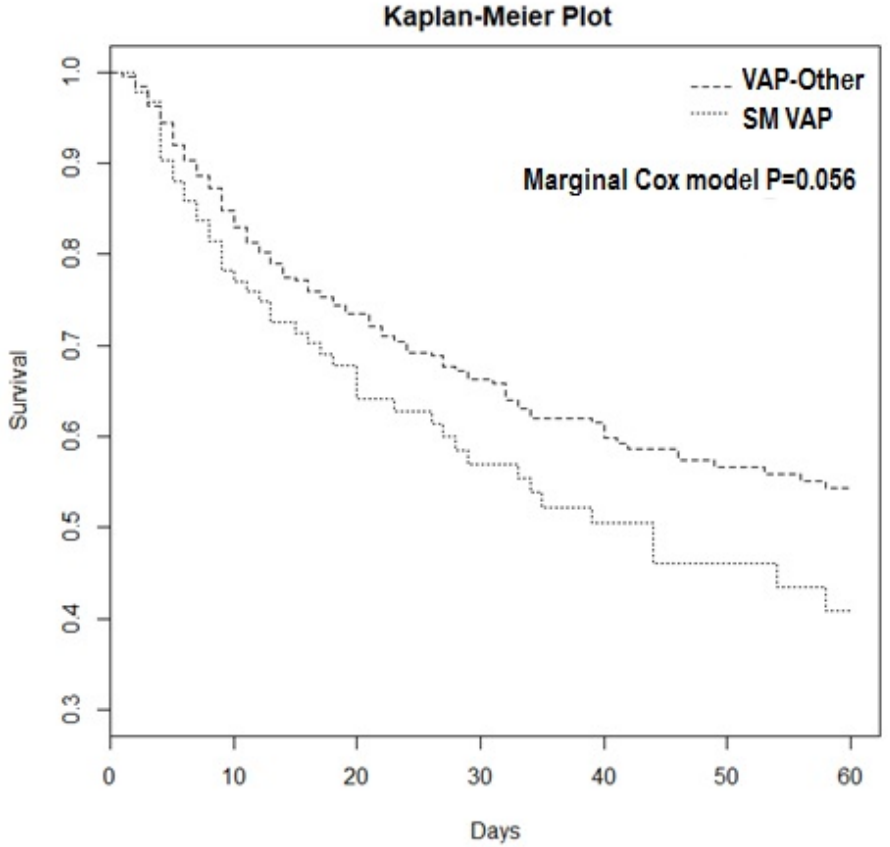


Figure 2: **Day-60 mortality according to VAP group**

Table 1: Baseline characteristics according to the type of VAP

Characteristic's	Other- VAP n=1 492	*SM*-VAP n=102	*Pyo*-VAP n=549	*P**	*P***
Age, median (IQR)	65 [53 - 74]	62 [52 - 75]	66 [53 - 75]	0.52	0.25
Male gender	1051 (70.4)	62 (60.8)	396 (72.1)	0.04	0.02
Diagnosis at the ICU admission (*missing n=12*)					
Organ Failure	64 (4.3)	4 (4)	25 (4.6)	<.01	<.01
Septic shock	179 (12.1)	24 (23.8)	77 (14.1)	.	.
Hemorrhagic shock	49 (3.3)	7 (6.9)	17 (3.1)	.	.
Cardiogenic shock	70 (4.7)	2 (2)	21 (3.8)	.	.
Others shock	33 (2.2)	1 (1)	13 (2.4)	.	.
Respiratory distress	535 (36.1)	37 (36.6)	216 (39.6)	.	.
COPD exacerbation	60 (4.1)	1 (1)	29 (5.3)	.	.
Acute renal failure	37 (2.5)	6 (5.9)	9 (1.6)	.	.
Coma	302 (20.4)	9 (8.9)	87 (15.9)	.	.
Continuous monitoring	89 (6)	8 (7.9)	33 (6)	.	.
Scheduled surgery	44 (3)	2 (2)	13 (2.4)	.	.
Trauma	19 (1.3)	0 (0)	6 (1.1)		
Co-morbidities	733 (49.1)	52 (51)	285 (51.9)	0.72	0.86
Chronic Hepatic failure	101 (6.8)	8 (7.8)	27 (4.9)	0.68	0.23
Chronic Heart failure	234 (15.7)	11 (10.8)	79 (14.4)	0.18	0.33
Chronic Respiratory failure	287 (19.2)	18 (17.6)	125 (22.8)	0.69	0.25
Chronic Renal failure	74 (5)	7 (6.9)	29 (5.3)	0.40	0.52
Chronic Immunodeficiency	247 (16.6)	20 (19.6)	95 (17.3)	0.42	0.58
Aplasia	31 (2.1)	6 (5.9)	10 (1.8)	0.01	0.01
Corticosteroids	95 (6.4)	6 (5.9)	35 (6.4)	0.85	0.85
Chemotherapy	106 (7.1)	9 (8.8)	44 (8)	0.52	0.78
HIV non AIDS	2 (0.1)	0 (0)	2 (0.4)	0.71	0.54
AIDS	38 (2.5)	1 (1)	11 (2)	0.32	0.48
Other	4 (0.3)	1 (1)	0 (0)	0.21	0.02
Transplant	29 (1.9)	3 (2.9)	11 (2)	0.49	0.55
Medical admission category	1119 (75.3)	75 (75.8)	426 (77.6)	0.91	0.69
SAPS II score at the admission , median (IQR)	49 [37 - 62]	52 [40 - 65]	50 [38 - 63]	0.11	0.25
GLASGOW effective (missing n=105)	8 [3 - 14]	7 [3 - 14]	8 [4 - 15]	0.26	0.08
SOFA scoring , median (IQR)	8 [5 - 10]	8.5 [6 - 12]	8 [5 - 10]	<.01	0.01
Respiratory component	2 [2 - 3]	3 [2 - 3]	2 [2 - 3]	0.52	0.78
Cardiovascular component	3 [1 - 4]	3 [1 - 4]	3 [1 - 4]	<.01	0.02
Neurological component	1 [0 - 3]	0 [0 - 3]	1 [0 - 3]	0.93	0.86
Liver component	0 [0 - 1]	0 [0 - 1]	0 [0 - 1]	0.13	0.06
Kidney component	0 [0 - 2]	0 [0 - 2]	1 [0 - 2]	0.74	0.88
Coagulation component	0 [0 - 1]	0 [0 - 2]	0 [0 - 1]	0.05	0.03
ICU admission to first VAP time (days)	9 [5 - 14]	12 [7 - 17]	10 [6 - 15]	<.01	0.03
Duration of ICU stay after the First VAP (days)	13 [7 - 24]	16.5 [8 - 33]	16 [9 - 31]	0.04	0.99
ICU overall length of stay (days)	24 [15 - 38]	32.5 [20 - 46]	29 [19 - 45]	<.01	0.37
Hospital length of stay (days), (missing n=64)	40 [24 - 66.5]	43 [30 - 64]	48 [29 - 76]	0.34	0.25

ICU mortality n (%)	473 (31.7)	40 (39.2)	184 (33.5)	0.12	0.27
Hospital mortality n (%)	636 (42.6)	54 (52.9)	242 (44.1)	0.04	0.10

P**:** Chi2 or Mann Whitney test comparing patient with other-VAP vs. SM-VAP ***P:** Chi2 or Mann Whitney Test comparing patient with *Pyo*-VAP vs *SM*-VAP; VAP: ventilator-associated pneumonia; *SM*-VAP: VAP due to *Stenotrophomonas maltophilia*; Pyo-VAP: VAP due to *Pseudomonasaeruginosa*; COPD: Chronic Obstructive Pulmonary Disease- SAPSII score: Simplified Acute Physiology Score- SOFA score: sequential organ failure assessment score

¤**Matching criteria** : same ICU, predicted hospital mortality assessed by SAPS II and delay before VAP

Table 2: Risk factors for ventilator-associated pneumonia due to Stenotrophomonas maltophilia

Variables[1]	OR IC 95%	*P**
SOFA Score 2 days before VAP		
Respiratory systems Score > 2	1.73 [1.02 -2.92]	0.04
Coagulation system Score > 2	2.93 [1.33 -6.48]	<.01
Antibiotic 1 week before VAP occurrence		
ureido/carboxypenicillin	2.08 [1.22 -3.55]	<.01
Carbapenems (Imipenem/meropenem)	3.20 [1.77- 5.79]	<.001

P *: logistic regression stratified in matched pair and selection stepwise for adjustments variables

SOFA score: sequential organ failure assessment score; VAP: ventilator associated penumonia

[1] Tested variables in the multivariate model: **At the admission**: male gender, chronic heart failure; **In the 2 days before VAP occurrence**: accidental extubation and SOFA scoring (coagulation and cardio-vascular); **In the week before VAP occurrence**: Ureido/carboxypenicillin, Glycopeptides, % Antibiotic received, parenteral nutrition, Dialysis, central venous catheter

Table 3: Risk factors of 30-day and 60-day mortality in ventilator-associated pneumonia due to Stenotrophomonas maltophilia

Characteristics	Alive up at Day-30 n=60)	Death before Day-30 (n=42)	HR IC 95%	*P*	Alive Up to Day-60 (n=52)	Death before Day-60 (n=50)	HR IC 95%	*P*
Age, median (IQR)	57 [50 - 69]	67 [60 - 78]	1.03 [1.01-1.05]	<.01	54.5 [48.5 - 64.5]	67.5 [60 - 78]	1.04 [1.02-1.06]	<.01
Male	39 (65)	23 (54.8)	0.65 [0.36-1.2]	0.17	32 (61.5)	30 (60)	0.77 [0.44-1.36]	0.37
Co-morbidities	26 (43.3)	26 (61.9)	1.77 [0.95-3.31]	0.07	22 (42.3)	30 (60)	1.70 [0.96-2.99]	0.07
Chronic Hepatic failure	3 (5)	5 (11.9)	1.59 [0.62-4.03]	0.33	2 (3.8)	6 (12)	1.68 [0.72-3.95]	0.23
Chronic Heart failure	2 (3.3)	9 (21.4)	3.15 [1.49-6.65]	<.01	2 (3.8)	9 (18)	2.71 [1.3-5.62]	<.01
Chronic Respiratory failure	10 (16.7)	8 (19)	1.32 [0.61-2.86]	0.48	9 (17.3)	9 (18)	1.26 [0.61-2.6]	0.53
Chronic Renal failure	5 (8.3)	2 (4.8)	0.65 [0.16-2.7]	0.56	4 (7.7)	3 (6)	0.91 [0.28-2.93]	0.87
Immunodeficiency	10 (16.7)	10 (23.8)	1.39 [0.68-2.82]	0.37	8 (15.4)	12 (24)	1.45 [0.76-2.78]	0.26
Medical admission category	45 (75)	30 (76.9)	1.14 [0.54-2.41]	0.72	40 (76.9)	35 (74.5)	1.04 [0.54-2.01]	0.90
SAPS II score at the admission, median (IQR)	49 [39.5 - 64.5]	58 [41 - 67]	1.01 [1-1.03]	0.11	48.5 [38.5 - 63]	55.5 [42 - 67]	1.01 [1-1.03]	0.12
Glasgow coma scale (missing n=12)	7 [3 - 15]	7 [3 - 13]	0.97 [0.91-1.03]	0.36	7 [3 - 15]	7 [3 - 13]	0.98 [0.92-1.04]	0.43
SOFA score at VAP onset, median (IQR)	8 [6 - 11]	10 [7 - 13]	1.06 [0.99-1.14]	0.12	8 [5.5 - 11]	10 [7 - 13]	1.05 [0.98-1.12]	0.16
Respiratory component	3 [1.5 - 3]	3 [2 - 3]	1.03 [0.82-1.31]	1.03	2.5 [1.5 - 3]	3 [2 - 3]	1.03 [0.83-1.28]	0.80
Cardiovascular component	3 [1 - 4]	4 [3 - 4]	1.15 [0.91-1.45]	0.24	3 [1 - 4]	3 [2 - 4]	1.06 [0.86-1.3]	0.60
Neurological component	0 [0 - 3]	1.5 [0 - 4]	1.11 [0.93-1.31]	0.25	0 [0 - 3]	0.5 [0 - 4]	1.06 [0.91-1.24]	0.44
Liver component	0 [0 - 1]	0 [0 - 2]	1.17 [0.89-1.54]	0.27	0 [0 - 0.5]	0 [0 - 2]	1.18 [0.91-1.52]	0.22
Kidneys component	0 [0 - 2]	0.5 [0 - 3]	1.03 [0.84-1.27]	0.78	0 [0 - 2]	1 [0 - 3]	1.06 [0.88-1.28]	0.53
Coagulation component	0 [0 - 1.5]	0 [0 - 2]	1.07 [0.85-1.36]	0.56	0 [0 - 1.5]	0 [0 - 2]	1.07 [0.86-1.33]	0.56
Treatment modality				0.43				0.56
Not Treated	45 (75)	25 (59.5)	0.71 [0.29-1.74]		38 (73.1)	32 (64)	0.91 [0.38-2.17]	
Monotherapy	9 (15)	11 (26.2)	1.11 [0.41-2.99]		8 (15.4)	12 (24)	1.31 [0.49-3.5]	
Combination therapy	6 (10)	6 (14.3)	1		6 (11.5)	6 (12)	1	

* Cox model; Time zero (T0): the SM-VAP occurrence

SAPSII score: Simplified Acute Physiology Score- **SOFA score**: sequential organ failure assessment score – **VAP:** ventilator-associated pneumonia:

Risk factors for *Stenotrophomonas maltophilia* VAP :

- Exposure to carbapenem and carboxy- or ureido-penicillin during the week before VAP
- The severity of disease with respiratory and hematological failures (SOFA respiratory and coagulation scores) 2 days before VAP occurrence

SM-VAP

Same mortality

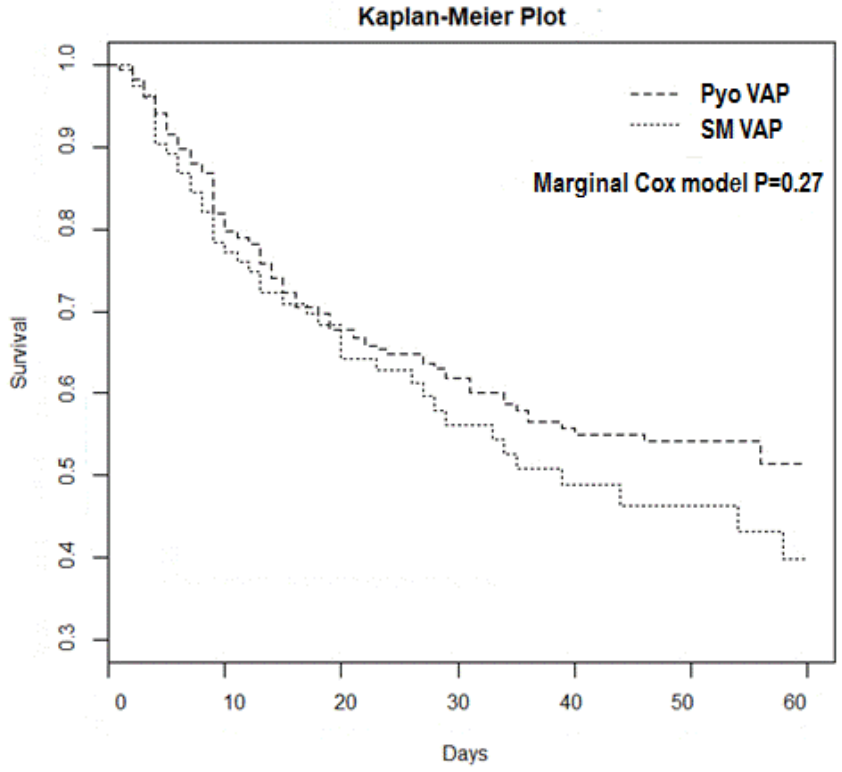
Pyo-VAP

Treatment modality and mortality 30-days in SM-VAP

SM-VAP

Non treated	Monotherapy	Combination therapy
0.71[0.29-1.74]	1.11[0.41-2.99]	1

HR IC 95%
Cox model stratified by center



***SM-VAP* mortality risk factors :**
Age and chronic heart failure