Risk Factors for a First Episode of Ventilator-Associated Pneumonia Caused by *Stenotrophomonas Maltophilia*

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Abstract

Background: The incidence of ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia* (SM-VAP) is on the rise. This pathology is associated with increased morbidity and mortality in intensive care unit (ICU), notably due to intrinsic resistance and ineffective probabilistic antibiotic therapy. Our study aimed to determine the risk factors for a first episode of SM-VAP in ICU.

Methods: This single center retrospective study was conducted from 2010 to 2018 in the polyvalent ICU of Félix Guyon University Hospital in Reunion Island. All patients who developed ventilator-associated pneumonia (VAP) during their ICU stay were consecutively evaluated. Patients with a first episode of SM-VAP were compared to those with a first episode of VAP caused by another microorganism.

Results: A total of 89 patients developed a first episode of SM-VAP over the study period. In the group of patients with SM-VAP, infection was polymicrobial in 43.8% of cases and ICU mortality was 49.4%. After multivariate logistic regression analysis, the risk factors for a first episode of SM-VAP were: chronic respiratory failure (Odds Ratio (OR): 4.212; 95% Confidence Interval (CI): 1.776 – 9.989; $p = 0.001$), chronic renal failure (OR: 2.693; 95% CI: 1.356 – 5.352; $p = 0.05$), use of third-generation cephalosporins active against *Pseudomonas aeruginosa* (OR 2.862; 95% CI: 1.505 – 5.442; $p = 0.001$), and female sex (OR: 2.646; 95% CI: 1.458 – 4.808; $p = 0.001$).

Conclusion: In our study, chronic respiratory failure, chronic renal failure, use of third-generation cephalosporins active against *P. aeruginosa*, and female sex were identified as risk factors for a first episode of SM-VAP.

Background

Stenotrophomonas maltophilia (SM) is a ubiquitous bacterium mainly responsible for opportunistic and nosocomial infections. This strictly aerobic, non-fermenting gram-negative bacillus (NF-GNB) has its natural reservoirs in water, soil, and plants. While SM is found in health care facility water systems, it can also survive on inert surfaces by producing biofilm on medical material, which then acts as a vector of nosocomial infection (1). Until about 15 years ago, SM was considered to be of low pathogenicity, with the literature reporting numerous cases of colonization with no prognostic impact on infected subjects (2).

Studies have highlighted the intrinsic resistance of SM to several antibiotics - including extended-spectrum antibiotics, which are usually administered to intensive care unit (ICU) patients with serious pulmonary infection as part of probabilistic antibiotic therapy (3). The main mechanisms involved are altered membrane permeability, efflux pumps, and the presence of inducible chromosomal beta-lactamases (4).

According to epidemiological surveillance studies, SM is now the third most common infection-causing NF-GNB, after *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (5,6). The prevalence of SM

infections is steadily increasing (4), the most frequent being respiratory tract infections. Depending on the series, the incidence of ICU-acquired pneumonia caused by SM varies between 0.37 and 2.0% (7–9). A recent study conducted in our ICU found an incidence of ventilator-associated pneumonia caused by *S. maltophilia* (SM-VAP) of 1.4% (10).

Infections with SM are now considered to be particularly severe. Attributable mortality has been shown to vary between 12.0 and 60.0% for all types of infection (6,7,11) and between 41.2 and 50.0% for pneumonia (including ventilator-associated pneumonia (VAP)) (8,9,12,13). The excess mortality due to SM in patients with VAP could be explained by delayed initiation of effective antibiotic therapy. Indeed, this microorganism is not specifically covered by recommendations for the management of VAP (14,15). In the 2008 meta-analysis by Kuti *et al.*, ineffective probabilistic antibiotic therapy was associated with increased mortality in patients with SM-VAP (16). Other series have since confirmed this trend (17–19).

In view of the above, this study aimed to determine the risk factors for a first episode of SM-VAP in ICU.

Methods

This single center retrospective study was conducted in the polyvalent ICU of Félix Guyon University Hospital in Reunion Island. All adult ICU patients who developed an episode of VAP between 1 January 2010 and 31 December 2018 were consecutively evaluated (Figure 1). Data on first episodes of VAP were retrospectively collected from the database of nosocomial infections of the French network *ReaRaisin*.

This study was approved by the Ethics Committee of the French Society of Infectious Disease and Tropical Medicine (CER-MIT 2021-0506) and was registered in the internal registry of treatment activities of Félix Guyon University Hospital (RCH-2021-0017). In accordance with the French legislation on non-interventional studies, the requirement for informed consent was waived owing to the retrospective nature of the study (20), this study agrees with the recommendations STROBE (*The Strengthening the Reporting of Observational Studies in Epidemiology*) (21).

Definitions

The diagnosis of pneumonia was confirmed in the presence of new or progressive radiological infiltrates associated with one of the following criteria: temperature > 38.5°C or < 36.0°C, white blood cell count >11G/L or <4G/L, purulent bronchial secretions, drop in oxygenation, and/or positive respiratory culture obtained by bronchoalveolar lavage, protected distal sampling, or endotracheal aspiration. Ventilator-associated pneumonia was defined by the onset of pneumonia at least 48 hours after mechanical ventilation (MV) initiation (22–24).

Antibiograms were performed using the disc diffusion method and interpreted according to EUCAST (*European Committee on Antimicrobial Susceptibility Testing*) susceptibility breakpoints: 10^4

colony forming unit (CFU)/mL for bronchoalveolar lavage, 10^3 CFU/mL for protected distal sampling, and 10^5 CFU/mL for endotracheal aspiration (25).

Data collection

The following information was collected:

- demographic data: age, sex.
- medical history: diabetes, hypertension, chronic heart failure, chronic respiratory disease (including chronic respiratory failure, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome, restrictive syndrome), chronic liver failure, chronic renal failure (clearance < 60 ml/mn/ 1.73m^2), immunodeficiency, cancerous pathology dating back less than three months, chronic alcohol abuse, body mass index (BMI) > 30 kg/m 2 , malnourishment (BMI < 18.5 kg/m 2 or weight loss $> 10\%$ over the previous 6 months).
- reason for admission to ICU.
- Sequential Organ Failure Assessment (SOFA) score on admission to ICU and on the day of VAP diagnosis.
- settings of MV.
- organ failure during ICU stay and on the day of VAP diagnosis.
- highest bilirubin level, lowest platelet count, lowest prothrombin level, and lowest PaO $_2$ /FiO $_2$ ratio during ICU stay; PaO $_2$ /FiO $_2$ ratio on the day of VAP diagnosis.
- use of organ support such as extracorporeal membrane oxygenation, renal replacement therapy, catecholamines.
- exposure data: prior corticosteroid therapy, prior rectal or respiratory colonization with SM, hospital stay in the last 6 months, type and duration of antibiotic therapy during ICU stay, parenteral nutrition during ICU stay, MV duration before VAP diagnosis.
- infection data: type of respiratory sample, type of infection (monomicrobial or polymicrobial), Clinical Pulmonary Infection Score (CPIS) on the day of VAP diagnosis, time to initiation of effective antibiotic therapy. Note that probabilistic antibiotic therapy was considered effective if at least one of the used molecules had *in vitro* activity against the isolated microorganism.
- prognosis: MV duration, tracheotomy, length of stay in ICU and in hospital, ICU and hospital mortality.

Statistical analyses

Results were expressed as number (percentage) for categorical variables and as median [25th-75th percentiles] for continuous variables. Categorical variables were compared using the chi-square test, the Kruskal-Wallis test, or Fisher's exact test, as appropriate. Continuous variables were compared using the nonparametric Mann-Whitney test.

Risk factors associated with a first episode of SM-VAP with a $p < 0.05$ in univariate analysis were entered into the multivariate logistic regression model. In cases of collinearity, only the most clinically relevant factors were entered in the multivariate model. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. The significance level was set at $p < 0.05$. Statistical analyses were performed using SAS statistical software (8.2, Cary, NC, USA).

Results

Study population

A total of 9,542 patients were admitted to the polyvalent ICU of Félix Guyon University Hospital between 1 January 2010 and 31 December 2018. Of these, 431 patients had an episode of VAP and were included in the analysis. *Stenotrophomonas maltophilia* was found in 20.6% ($n = 89$) of respiratory samples (Figure 1).

The main reasons for admission to ICU were acute respiratory failure (44.9%), cardiogenic shock (16.7%), postoperative complications (15.5%), septic shock (12.9%), neurological failure (11.1%), and severe trauma (5.1%).

Included patients were predominantly male (71.7%) and median age was 60 years [48-70]. The median SOFA score on ICU admission was 10 [7-12].

The clinical and demographic characteristics of included patients are listed in Table 1.

Diagnosis and microbiological characteristics of VAP

The median MV duration before VAP diagnosis was 10 days [5-15] in patients infected with SM compared to 7 days [4-11] in patients infected with another microorganism ($p = 0.001$). The median SOFA score on the day of VAP diagnosis was 9 [4-12] in patients infected with SM versus 8 [5-11] in patients infected with another microorganism ($p = 0.726$).

Respiratory samples were obtained by protected distal sampling in 46.8% of cases, endotracheal aspiration in 34.5% of cases, and bronchoalveolar lavage in 18.7% of cases.

The most frequently identified microorganisms in patients without SM infection were: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Escherichia coli*, *Enterobacter aerogenes*, and *Acinetobacter baumannii* (Table 2).

The prevalence of polymicrobial infection in patients infected with SM was 43.8%, with the most common co-infecting microorganism being *P. aeruginosa* (Table 3). The prevalence of polymicrobial infection in patients infected with another microorganism was 34.5%.

Identified SM strains had an identical rate of susceptibility of 84.2% to trimethoprim-sulfamethoxazole and to fluoroquinolones. The rate of susceptibility to other antibiotics was lower, namely 61.8% for ticarcillin-clavulanate and 39.3% for ceftazidime. Probabilistic antibiotic therapy was effective against SM in 66.3% of cases. In the control group, probabilistic antibiotic therapy was effective against the identified microorganism in 94.2% of cases ($p < 0.001$).

Risk factors for SM-VAP in univariate analysis

The patient characteristics significantly associated with an increased risk of developing a first episode of SM-VAP in univariate analysis were: female sex ($p = 0.001$), chronic respiratory disease ($p = 0.013$), chronic renal failure ($p = 0.038$), and malnourishment ($p < 0.001$) (Table 1).

The other variables significantly associated with an increased risk of developing a first episode of SM-VAP in univariate analysis were: prior corticosteroid therapy ($p < 0.001$), prior rectal colonization with SM ($p < 0.027$), MV duration before SM-VAP diagnosis ($p = 0.001$), number of different antibiotics used ($p < 0.001$), use of third-generation cephalosporins active against *Pseudomonas aeruginosa* ($p = 0.044$), use of carbapenems ($p < 0.001$), use of glycopeptides ($p = 0.01$), use of fluoroquinolones ($p = 0.01$), use of linezolid ($p < 0.001$), use of trimethoprim-sulfamethoxazole ($p = 0.044$), use of aminoglycosides ($p < 0.001$), use of antifungals ($p < 0.001$), use of antihistamines ($p < 0.001$), use of parenteral nutrition ($p < 0.001$), and use of renal replacement therapy ($p < 0.001$) (Table 4).

Risk factors for SM-VAP in multivariate analysis

The variables independently associated with an increased risk of developing a first episode of SM-VAP in multivariate analysis were: chronic respiratory disease (Odds Ratio (OR) 4.212; 95% Confidence Interval (CI): 1.776 – 9.989; $p = 0.001$), chronic renal failure (OR 2.693; 95% CI: 1.356 – 5.352; $p = 0.05$), use of third-generation cephalosporins active against *Pseudomonas aeruginosa* (OR 2.862; 95% CI: 1.505 – 5.442; $p = 0.001$), and female sex (OR 2.646; 95% CI: 1.458 – 4.808; $p = 0.001$) (Table 5).

Discussion

To our knowledge, this study is the first to evaluate the risk factors for a first episode of SM-VAP. The following risk factors were identified: chronic respiratory disease, chronic renal failure, use of third-generation cephalosporins active against *Pseudomonas aeruginosa*, and female sex.

Earlier studies also found the use of third-generation cephalosporins active against *P. aeruginosa* to be a risk factor for SM-VAP (26,27). Thus, in the study by Hanes *et al.*, the administration of cefepime was significantly associated with the occurrence of SM-VAP (OR 3.31 [1.12 - 9.72]). Interestingly, the number of patients evaluated in that study was small, which reinforces the association between the two

events (26). More recently, Imoto *et al.* found a significant association between the use of third-generation cephalosporins active against *P. aeruginosa* and the occurrence of hospital-acquired pneumonia caused by SM (27).

Our analysis found no association between the use of carbapenems and the occurrence of SM-VAP. By contrast, in their 2019 case-control study of 102 patients, Ibn Saied *et al.* identified exposure to carbapenems as a risk factor for this infection (OR 3.20 [1.77- 5.79]). We initially explained the difference between these and our findings by the fact that the use of carbapenem was lower in our patients since only first episodes of VAP were included in our analysis. Yet, on closer examination, we found that the percentage of patients who received carbapenems in our study was comparable to that in the study by Ibn Saied *et al.* (8).

No association was found in our study between the use of aminoglycosides and the occurrence of SM-VAP. While Van Couvenberghe *et al.* did find an association between these two events in their 1997 study, their sample was small and included only 25 cases of SM-VAP (28).

In line with published data, we found no association between other types of antibiotic therapy and the occurrence of SM-VAP. However, some studies identified exposure to fluoroquinolones as a risk factor for hospital-acquired pneumonia caused by NF-GNB (29,30), and others highlighted an association between this antibiotic and multidrug-resistant SM infection (31–33). While the use of glycopeptides has been identified as a risk factor for bacteremia caused by NF-GNB (34), to our knowledge no association has been reported between this antibiotic and the occurrence of SM-PAVM. In our study, few patients received glycopeptides due to the absence of methicillin-resistant *S. aureus* and, more generally, due to the rarity of this microorganism in the ecology of our ICU. Interestingly, no association was found between glycopeptides and SM-VAP in the study by Ibn Saied *et al.*, whose population was similar to ours yet was more frequently treated with this antibiotic (8).

To date, no association has been reported between malnourishment and SM-VAP. However, some studies suggest that parenteral nutrition is a risk factor for SM infection (8,35). Others indicate that the use of parenteral nutrition in ICU has been declining in recent years and currently concerns less than 10% of ICU patients (36). In our study, 9% of patients required parenteral nutrition during their stay in ICU. While we found parenteral nutrition to be significantly higher in patients with SM-PAV, we were unable to determine the impact of this treatment on the occurrence of the infection.

Rectal colonization with SM was not a risk factor for SM-VAP in our patients, which is in line with published data. However, one study found the risk of developing an infection with SM to increase in cases of relative abundance in the oral area (37) – a parameter that was not analyzed in our study. More generally, several studies have highlighted an association between digestive colonization with the NF-GNB *Acinetobacter baumannii* or *Pseudomonas aeruginosa* and infection in ICU (38–40).

In our study, chronic renal failure and chronic respiratory failure were independent risk factors for SM-VAP. No such association has been reported in the literature to date. Our finding may be explained by the high

prevalence of chronic renal failure in our study population (16.9%). In a recent comparable study, this prevalence varied between 4.5 and 7.1% depending on the group (8). Note that the prevalence of diabetes in our study population was also high at 34.3%, which is much higher than the prevalence reported for the general French population (41).

No association has been reported to date between chronic respiratory disease and the occurrence of SM-VAP. It is established, however, that patients with chronic respiratory disease such as cystic fibrosis and COPD are more likely than the general population to carry multidrug-resistant microorganisms, and in particular NF-GNB. In cystic fibrosis patients, the most common microorganism is *P. aeruginosa* and other NF-GNB are increasingly being detected (42–45). Fewer data are available on the bacterial ecology of patients with COPD. We found only one study comparing patients with and without COPD who developed VAP during their stay in ICU: while the incidence of VAP was the same in both groups, that of *E. coli* and SM was significantly higher in patients with COPD (46).

In our study, the incidence of a first episode of SM-VAP was 0.93%. This is higher than figures reported in the literature, with two recent studies reporting incidences of 0.27 and 0.48%, respectively (8,9). While the incidence of SM in the respiratory tract was 2% in the study by Nseir *et al.*, this figure included both colonization and infection cases (7). Some studies have shown that patients living in tropical environments are at greater risk of developing pneumonia caused by NF-GNB, and in particular by *A. baumannii* (47,48). Interestingly, pneumonia caused by *A. baumannii* was common in our control group, as it represented 5.8% of monomicrobial infections and 11.9% of polymicrobial infections. One study conducted in Reunion Island reported a high prevalence of *A. baumannii* in non-human reservoirs outside hospital and suggested a link with the high prevalence of pneumonia caused by *A. baumannii* in the Reunionese population (49). This could explain not only the high incidence of infections with *A. baumannii* in our study population, but also that of infections with SM given the similarities between the two microorganisms.

In our study, almost half of patients with a first episode of SM-VAP (49.4%) died in ICU, and an even higher percentage (57.3%) died before hospital discharge. This finding is in line with published data, with studies reporting an ICU mortality ranging from 41.3 to 50%. (9,12,13,50,51). However, in the 2002 study by Hanes *et al.*, ICU mortality (23.1%) was much lower than in our study (26). This difference may be explained by the fact that their study population (median age of 47 years) was much younger than ours (median age of 60 years) and was composed of severe trauma patients with fewer comorbidities. Other studies also reported lower ICU mortality, but for smaller cohorts (6,7).

The excess mortality due to SM in our patients may be explained by delayed initiation of effective antibiotic therapy. Indeed, probabilistic antibiotic therapy was active against SM in only 66.3% of our patients with SM-VAP, whereas it was active against the identified microorganism in 94.2% of patients in the control group. Several authors have highlighted an association between ineffective antibiotic therapy and mortality in patients with hospital-acquired pneumonia caused by SM (12,16,17,19). In particular,

some studies on SM-VAP have reported significantly higher mortality in patients receiving initial antibiotic therapy inactive against SM (6,7,25).

In patients with polymicrobial SM-VAP, probabilistic antibiotic therapy was effective against the co-infecting microorganism in 100% of cases and against SM in less than 50% of cases (18/39). Interestingly, studies on infection with SM report excess mortality in patients co-infected with *P. aeruginosa* (52). In our study, *P. aeruginosa* was the most common co-infecting microorganism (28.2% of patients with polymicrobial SM-VAP), which could also explain, at least in part, the high mortality observed in our study population.

The main limitation of our study is its retrospective nature, which could have introduced biases. Since our study was conducted in a single center, our results cannot necessarily be extrapolated to other centers. While our diagnostic criteria were very strict, many of the evaluated cases of SM-VAP were polymicrobial infections, which may have led to a bias in the analysis of risk factors for developing a first episode SM-VAP. Another limitation of our study is the high percentage of patients with co-morbidities (especially cardiovascular) compared to other studies on SM-VAP.

Conclusion

In our study, chronic respiratory disease, chronic renal failure, use of third-generation cephalosporins active against *P. aeruginosa*, and female sex were identified as risk factors for a first episode of SM-VAP. Moreover, SM was associated with excess mortality, as was the case in other studies on hospital-acquired pneumonia. This excess mortality could be explained by delayed initiation of effective antibiotic therapy, itself due to the resistance profile of SM and the difficulty in identifying patients at risk of infection. Future studies considering the risk factors identified in our work could evaluate the impact on mortality of using effective antibiotic therapy early in patients with SM-VAP.

Abbreviations

SM: *Stenotrophomonas maltophilia*

VAP: ventilator-associated pneumonia

SM-VAP: ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*

NF-GNB: non-fermenting gram-negative bacillus

ICU: intensive care unit

MV: mechanical ventilation

CFU: colony forming unit

BMI: body mass index

SOFA score: Sequential Organ Failure Assessment score

CPIS: Clinical Pulmonary Infection Score

OR: Odds Ratio

CI: Confidence Interval

COPD: chronic obstructive pulmonary disease

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the French Society of Infectious Disease and Tropical Medicine (CER-MIT 2021-0506) and was registered in the internal registry of treatment activities of Félix Guyon University Hospital (RCH-2021-0017). In accordance with the French legislation on non-interventional studies, the requirement for informed consent was waived owing to the retrospective nature of the study. This study agrees with the recommendations STROBE.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CC collected, analyzed, interpreted the data from this research and was a major contributor in writing the manuscript. BP collected, analyzed, interpreted the data from this research and was a major contributor in writing the manuscript. LT collected the data from this research. NA analyzed and interpreted the data from this research.

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References

1. SITE DE MICROBIOLOGIE MEDICALE [Internet]. [cité 3 mai 2020]. Disponible sur: <http://www.microbes-edu.org/index.html>
2. Pathmanathan A, Waterer GW. Significance of positive *Stenotrophomonas maltophilia* culture in acute respiratory tract infection. *Eur Respir J*. mai 2005;25(5):911-4.
3. Adegoke AA, Stenström TA, Okoh AI. *Stenotrophomonas maltophilia* as an Emerging Ubiquitous Pathogen: Looking Beyond Contemporary Antibiotic Therapy. *Front Microbiol*. 2017;8:2276.
4. Chang Y-T, Lin C-Y, Chen Y-H, Hsueh P-R. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol*. 2015;6:893.
5. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial Susceptibility of *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* Complex and *Stenotrophomonas maltophilia* Clinical Isolates: Results From the SENTRY Antimicrobial Surveillance Program (1997-2016). *Open Forum Infect Dis*. mars 2019;6(Suppl 1):S34-46.
6. Fihman V, Le Monnier A, Corvec S, Jaureguy F, Tankovic J, Jacquier H, et al. *Stenotrophomonas maltophilia*—the most worrisome threat among unusual non-fermentative gram-negative bacilli from hospitalized patients: a prospective multicenter study. *J Infect*. avr 2012;64(4):391-8.
7. Nseir S, Di Pompeo C, Brisson H, Dewavrin F, Tissier S, Diarra M, et al. Intensive care unit-acquired *Stenotrophomonas maltophilia*: incidence, risk factors, and outcome. *Crit Care*. 2006;10(5):R143.
8. Ibn Saïed W, Merceron S, Schwebel C, Le Monnier A, Oziel J, Garrouste-Orgeas M, et al. Ventilator-associated pneumonia due to *Stenotrophomonas maltophilia*: Risk factors and outcome. *J Infect*. mars 2020;80(3):279-85.
9. Guerci P, Bellut H, Mokhtari M, Gaudefroy J, Mongardon N, Charpentier C, et al. Outcomes of *Stenotrophomonas maltophilia* hospital-acquired pneumonia in intensive care unit: a nationwide retrospective study. *Crit Care*. 21 2019;23(1):371.
10. Puech B, Canivet C, Teyssere L, Miltgen G, Aujoulat T, Caron M, et al. Effect of antibiotic therapy on the prognosis of ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*. *Ann Intensive Care*. 26 nov 2021;11(1):160.

11. Falagas ME, Kastoris AC, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Dimopoulos G. Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. *Future Microbiol.* nov 2009;4(9):1103-9.
12. Tseng C-C, Fang W-F, Huang K-T, Chang P-W, Tu M-L, Shiang Y-P, et al. Risk factors for mortality in patients with nosocomial *Stenotrophomonas maltophilia* pneumonia. *Infect Control Hosp Epidemiol.* déc 2009;30(12):1193-202.
13. Xun M, Zhang Y, Li B-L, Wu M, Zong Y, Yin Y-M. Clinical characteristics and risk factors of infections caused by *Stenotrophomonas maltophilia* in a hospital in northwest China. *J Infect Dev Ctries.* 13 août 2014;8(8):1000-5.
14. Leone M, Bouadma L, Bouhemad B, Brissaud O, Dauter S, Gibot S, et al. Hospital-acquired pneumonia in ICU. *Anaesth Crit Care Pain Med.* févr 2018;37(1):83-98.
15. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical Infectious Diseases.* 1 sept 2016;63(5):e61-111.
16. Kuti EL, Patel AA, Coleman CI. Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: a meta-analysis. *J Crit Care.* mars 2008;23(1):91-100.
17. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest.* juill 2002;122(1):262-8.
18. Mueller EW, Hanes SD, Croce MA, Wood GC, Boucher BA, Fabian TC. Effect from multiple episodes of inadequate empiric antibiotic therapy for ventilator-associated pneumonia on morbidity and mortality among critically ill trauma patients. *J Trauma.* janv 2005;58(1):94-101.
19. Kollef KE, Schramm GE, Wills AR, Reichley RM, Micek ST, Kollef MH. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria. *Chest.* août 2008;134(2):281-7.
20. Toulouse E, Masseguin C, Lafont B, McGurk G, Harboun A, Roberts J, et al. French legal approach to clinical research. *Anaesth Crit Care Pain Med.* déc 2018;37(6):607-14.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 20 oct 2007;370(9596):1453-7.
22. Hubmayr RD, Burchardi H, Elliot M, Fessler H, Georgopoulos D, Jubran A, et al. Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia—Chicago, Illinois, May

2002. Intensive Care Med. nov 2002;28(11):1521-36.

23. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J. 2017;50(3).

24. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic « blind » bronchoalveolar lavage fluid. Am Rev Respir Dis. mai 1991;143(5 Pt 1):1121-9.

25. CASFM / EUCAST 2019 [Internet]. Société Française de Microbiologie. 2019 [cité 3 mai 2020]. Disponible sur: <https://www.sfm-microbiologie.org/2019/01/07/casfm-eucast-2019/>

26. Hanes SD, Demirkan K, Tolley E, Boucher BA, Croce MA, Wood GC, et al. Risk factors for late-onset nosocomial pneumonia caused by *Stenotrophomonas maltophilia* in critically ill trauma patients. Clin Infect Dis. 1 août 2002;35(3):228-35.

27. Imoto W, Yamada K, Kuwabara G, Yamairi K, Shibata W, Oshima K, et al. In which cases of pneumonia should we consider treatments for *Stenotrophomonas maltophilia*? J Hosp Infect. mai 2021;111:169-75.

28. VanCouwenberghe CJ, Farver TB, Cohen SH. Risk factors associated with isolation of *Stenotrophomonas* (*Xanthomonas*) *maltophilia* in clinical specimens. Infect Control Hosp Epidemiol. mai 1997;18(5):316-21.

29. Kim T, Chong YP, Park SY, Jeon M-H, Choo EJ, Chung J-W, et al. Risk factors for hospital-acquired pneumonia caused by carbapenem-resistant Gram-negative bacteria in critically ill patients: a multicenter study in Korea. Diagn Microbiol Infect Dis. avr 2014;78(4):457-61.

30. Leroy O, d'Escrivan T, Devos P, Dubreuil L, Kipnis E, Georges H. Hospital-acquired pneumonia in critically ill patients: factors associated with episodes due to imipenem-resistant organisms. Infection. juin 2005;33(3):129-35.

31. Ansari SR, Hanna H, Hachem R, Jiang Y, Rolston K, Raad I. Risk factors for infections with multidrug-resistant *Stenotrophomonas maltophilia* in patients with cancer. Cancer. 15 juin 2007;109(12):2615-22.

32. Wang C-H, Lin J-C, Chang F-Y, Yu C-M, Lin W-S, Yeh K-M. Risk factors for hospital acquisition of trimethoprim-sulfamethoxazole resistant *Stenotrophomonas maltophilia* in adults: A matched case-control study. J Microbiol Immunol Infect. oct 2017;50(5):646-52.

33. Wu R-X, Yu C-M, Hsu S-T, Wang CH. Emergence of concurrent levofloxacin- and trimethoprim/sulfamethoxazole-resistant *Stenotrophomonas maltophilia*: Risk factors and antimicrobial

- sensitivity pattern analysis from a single medical center in Taiwan. *J Microbiol Immunol Infect.* 13 janv 2021;
34. Rattanaumpawan P, Ussavasodhi P, Kiratisin P, Aswapokee N. Epidemiology of bacteremia caused by uncommon non-fermentative gram-negative bacteria. *BMC Infect Dis.* 8 avr 2013;13:167.
35. Mutlu M, Yılmaz G, Aslan Y, Bayramoğlu G. Risk factors and clinical characteristics of *Stenotrophomonas maltophilia* infections in neonates. *J Microbiol Immunol Infect.* déc 2011;44(6):467-72.
36. Barnoud D. Place de la nutrition parentérale en réanimation. *Réanimation.* août 2009;18(6):493-500.
37. Aitken SL, Sahasrabhojane PV, Kontoyiannis DP, Savidge TC, Arias CA, Ajami NJ, et al. Alterations of the Oral Microbiome and Cumulative Carbapenem Exposure Are Associated With *Stenotrophomonas maltophilia* Infection in Patients With Acute Myeloid Leukemia Receiving Chemotherapy. *Clin Infect Dis.* 4 mai 2021;72(9):1507-13.
38. Cobos-Trigueros N, Solé M, Castro P, Torres JL, Hernández C, Rinaudo M, et al. Acquisition of *Pseudomonas aeruginosa* and its resistance phenotypes in critically ill medical patients: role of colonization pressure and antibiotic exposure. *Crit Care.* 4 mai 2015;19:218.
39. Corbella X, Pujol M, Ayats J, Sendra M, Ardanuy C, Domínguez MA, et al. Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant *Acinetobacter baumannii*. *Clin Infect Dis.* août 1996;23(2):329-34.
40. Gómez-Zorrilla S, Camoez M, Tubau F, Cañizares R, Periche E, Dominguez MA, et al. Prospective observational study of prior rectal colonization status as a predictor for subsequent development of *Pseudomonas aeruginosa* clinical infections. *Antimicrob Agents Chemother.* sept 2015;59(9):5213-9.
41. Les chiffres du diabète en France | Fédération Française des Diabétiques [Internet]. [cité 4 août 2021]. Disponible sur: <https://www.federationdesdiabetiques.org/information/diabete/chiffres-france>
42. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med.* 15 oct 2003;168(8):918-51.
43. Surette MG. The cystic fibrosis lung microbiome. *Ann Am Thorac Soc.* janv 2014;11 Suppl 1:S61-65.
44. Davies JC, Rubin BK. Emerging and unusual gram-negative infections in cystic fibrosis. *Semin Respir Crit Care Med.* juin 2007;28(3):312-21.
45. Rajan S, Saiman L. Pulmonary infections in patients with cystic fibrosis. *Semin Respir Infect.* mars 2002;17(1):47-56.

46. Rouzé A, Boddaert P, Martin-Loeches I, Pova P, Rodriguez A, Ramdane N, et al. Impact of Chronic Obstructive Pulmonary Disease on Incidence, Microbiology and Outcome of Ventilator-Associated Lower Respiratory Tract Infections. *Microorganisms*. 23 janv 2020;8(2):E165.
47. Davis JS, McMillan M, Swaminathan A, Kelly JA, Piera KE, Baird RW, et al. A 16-year prospective study of community-onset bacteremic *Acinetobacter* pneumonia: low mortality with appropriate initial empirical antibiotic protocols. *Chest*. oct 2014;146(4):1038-45.
48. Dexter C, Murray GL, Paulsen IT, Peleg AY. Community-acquired *Acinetobacter baumannii*: clinical characteristics, epidemiology and pathogenesis. *Expert Rev Anti Infect Ther*. mai 2015;13(5):567-73.
49. Pailhories H. Réservoirs extra-hospitaliers et non-humains d'*Acinetobacter baumannii* sur l'île de la Réunion [Internet] [phdthesis]. Université d'Angers; 2016 [cité 28 juin 2021]. Disponible sur: <https://tel.archives-ouvertes.fr/tel-01442221>
50. Saugel B, Eschermann K, Hoffmann R, Hapfelmeier A, Schultheiss C, Phillip V, et al. *Stenotrophomonas maltophilia* in the respiratory tract of medical intensive care unit patients. *Eur J Clin Microbiol Infect Dis*. juill 2012;31(7):1419-28.
51. Gopalakrishnan R, Hawley HB, Czachor JS, Markert RJ, Bernstein JM. *Stenotrophomonas maltophilia* infection and colonization in the intensive care units of two community hospitals: A study of 143 patients. *Heart & Lung*. mars 1999;28(2):134-41.
52. Yin C, Yang W, Meng J, Lv Y, Wang J, Huang B. 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*. nov 2017;36(11):2231-5.

Tables

Table 1 : Clinical and demographic characteristics of study patients

Variables	Total (n=431)	Other VAP (n= 342)	SM VAP (n=89)	<i>p</i>
Gender, male	309 (71.7)	258 (75.4)	51 (57.3)	0.001
Age, years	60 [48-70]	60 [48-70]	59 [51-70]	0.67
SOFA score on the day of ICU admission	10 [7-12]	10 [7-12]	9 [7-12]	0.407
SOFA score on the day of VAP diagnosis	8 [5-11]	8 [5-11]	9 [4-12]	0.726
Comorbidities				
Chronic heart failure	149 (34.6)	115 (33.6)	34 (38.2)	0.453
Chronic respiratory disease	48 (11.1)	31 (9.1)	17 (19.1)	0.013
Chronic renale failure	73 (16.9)	51 (14.9)	22 (24.7)	0.038
Hypertension	229 (53.1)	184 (53.8)	45 (50.6)	0.634
Diabetes	148 (34.3)	118 (34.5)	30 (33.7)	0.99
Obesity	95 (22)	73 (21.3)	22 (24.7)	0.477
Denutrition	58 (13.5)	33 (9.6)	25 (28.1)	< 0.001
Chronic alcohol abuse	126 (29.2)	99 (28.9)	27 (30.3)	0.795
Chronic hepatic failure	24 (5.6)	15 (4.4)	9 (10.1)	0.064
Recent or ongoing chemotherapy	48 (11.1)	39 (11.4)	9 (10.1)	0.851
Immunodeficiency	49 (11.4)	44 (12.9)	5 (5.6)	0.061
Outcome				
ICU overall lenght of stay, days	20 [12-29]	19 [12-29]	21 [14-32]	0.272
ICU mortality	143 (33.2)	99 (28.9)	44 (49.4)	< 0.001
Hospital mortality	176 (40.8)	125 (36.5)	51 (57.3)	0.001

VAP = Ventilator Associated peumonia, SM VAP = ventilator-associated pneumonia caused by Stenotrophomonas maltophilia, SOFA score = Sequential Organ Failure Assessment score, ICU = intensive care unit

Results are expressed as median [25th–75th] percentiles or number.

Table 2 : Microbiological characteristics of VAP caused by an organism other than SM

	Monomicrobial infection n=224 (65.5%)	Polymicrobial infection n=118 (34.5%)
<u>Gram-negative bacillus</u>		
NF - GNB		
<i>Pseudomonas aeruginosa</i>	82 (36.6%)	41 (34.7%)
<i>Acinetobacter baumannii</i>	13 (5.8%)	14 (11.9%)
<i>Burkholderia cepacia</i>	3 (1.3%)	6 (5%)
<i>Other non fermenting GNB</i>	8 (3.6%)	3 (2.5%)
Enterobacteria		
<i>Escherichia coli</i>	17 (7.6%)	15 (12.7%)
<i>Proteus mirabilis</i>	3 (1.3%)	9 (7.6%)
<i>Klebsiella pneumoniae</i>	18 (8%)	34 (28.8%)
<i>Citrobacter koseri</i>	3 (1.3%)	6 (5%)
<i>Enterobacter cloacae</i>	20 (8.9%)	21 (17.8%)
<i>Enterobacter aerogenes</i>	11 (4.9%)	16 (13.5%)
<i>Serratia marcescens</i>	8 (3.6%)	7 (5.9%)
<i>Morganella spp.</i>	2 (0.89%)	6 (5%)
<i>Other enterobacteria</i>	8 (3.6%)	10 (8.5%)
Other GNB		
<i>Haemophilus spp.</i>	3 (1.3%)	12 (10.2%)
<u>Gram-positive cocci</u>		
<i>Staphylococcus aureus</i>	23 (10.3%)	32 (27.1%)
<i>Staphylococcus epidermidis</i>	-	2 (1.7%)
<i>Streptococcus pneumoniae</i>	1 (0.44%)	5 (4.2%)
<i>Enterococcus faecalis</i>	1 (0.44%)	2 (1.7%)

VAP = ventilator associated pneumonia, SM = *Stenotrophomonas maltophilia*, NF-GNB = non-fermenting gram-negative bacillus, GNB = gram-negative bacillus

Table 3 : Microbiological characteristics of SM-VAP

Variables	Total (n=89)
Monomicrobial infection (n,(%))	50 (56.17)
Polymicrobial infection (n,(%))	39 (43.83)
<i>Pseudomonas aeruginosa</i>	11
<i>Acinetobacter spp.</i>	5
<i>Escherichia coli</i>	2
<i>Proteus mirabilis</i>	2
<i>Klebsiella spp.</i>	6
<i>Serratia spp.</i>	2
<i>Enterobacter spp.</i>	6
<i>Morganella spp.</i>	1
<i>Citrobacter spp.</i>	1
<i>Staphylococcus spp.</i>	6
<i>Enterococcus spp.</i>	3
<i>Candida spp.</i>	8

SM-VAP = ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia*

Table 4 : Risk factors associated with SM-VAP assessed in uni-variate analysis

Variables	TOTAL (n=431)	Other VAP (n= 342)	SM VAP (n=89)	<i>p</i>
Duration of mechanical ventilation before infection	7 [5-12]	7 [4-11]	10 [5-15]	0.001
Number of different antibiotics received before infection	2 [1-2]	2 [1-3]	3 [2-5]	< 0.001
Beta lactams	47 (10.9)	34 (9.9)	13 (14.6)	0.411
Beta lactams + BLI	216 (50.1)	157 (45.9)	59 (66.3)	0.753
Third generation cephalosporins not active on <i>P. aeruginosa</i>	140 (32.5)	107 (31.3)	33 (37.1)	0.346
Third generation cephalosporins active on <i>P. aeruginosa</i>	11 (2.6)	6 (1.8)	5 (5.6)	0.044
Carbapenemes	73 (16.9)	41 (12)	32 (36)	< 0.001
Glycopeptides	41 (9.5)	22 (6.4)	19 (21.3)	< 0.001
Fluoroquinolones	39 (9)	25 (7.3)	14 (15.7)	0.01
Linezolid	26 (6)	13 (3.8)	13 (14.6)	< 0.001
Trimethoprim-sulfamethoxazole	11 (2.6)	6 (1.8)	5 (5.6)	0.044
Aminoglycosides	141 (32.7)	89 (26)	52 (58.4)	< 0.001
Antifungals	20 (4.6)	6 (1.8)	14 (15.7)	< 0.001
Metronidazole	60 (13.9)	43 (12.6)	17 (19.1)	0.076
Corticosteroids	92 (21.3)	62 (18.1)	30 (33.7)	< 0.001
Antihistamines	21 (4.9)	8 (2.4)	13 (14.6)	< 0.001
Parenteral nutrition	39 (9)	12 (3.6)	27 (30.3)	< 0.001
Rectal colonization with SM	22 (5.1)	13 (3.8)	9 (10.1)	0.027
Hospitalization in the last six months	253 (58.7)	199 (58.2)	54 (60.7)	0.718

VAP = ventilator-associated pneumonia, SM-VAP = ventilator-associated pneumonia caused by Stenotrophomonas maltophilia, BLI = beta-lactam inhibitors, SM = Stenotrophomonas maltophilia

Results are expressed as median [25th-75th] percentiles or number.

Table 5 : Risk factors independently associated with the occurrence of SM-VAP after multivariate analysis

Variables	Adjusted Odd Ratio [CI 95%]	<i>p</i>
Male	0.378 [0.208 – 0.686]	0.001
Chronic respiratory disease	4.212 [1.776 – 9.989]	0.001
Chronic renale failure	2.693 [1.356 – 5.352]	0.005
Third generation cephalosporins active on <i>P. aeruginosa</i>	2.852 [1.505 – 5.442]	0.001

SM-VAP = ventilator-associated pneumonia caused by Stenotrophomonas maltophilia

The Hosmer-Lemeshow test shows a good calibration of the model ($p = 0.676$).

The Nagelkerke and Cox / Snell R^2 are 0.23 and 0.15 respectively.

Figures

Figure 1 :

Figure 1

Flowchart

*ICU = intensive care unit, VAP = ventilator-associated pneumonia, SM-VAP = ventilator-associated pneumonia caused by *Stenotrophomonas maltophilia**