International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 10; Issue 02 (B); February 2021; Page No.23877-23882
DOI: http://dx.doi.org/10.24327/ijcar.2021.23882.4731

Research Article

STENOTROPHOMONAS MATOPHILIA BACTEREMIA IN ELDERLY PATIENTS IN THE SOUTHERN OF VIETNAM: PATIENT CHARACTERISTIC, ANTIBIOTICS RESISTANCE AND TREATMENT OUTCOME

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A R T I C L E I N F O

Article History:
Received 6th November, 2020
Received in revised form 15th December, 2020
Accepted 12th January, 2021
Published online 28th February, 2021

Key words:

Bacteremia, *Stenotrophomonas maltophilia*, antibiotic resistance, risk factor.

A B S T R A C T

Background: *Stenotrophomonas maltophilia* bacteremia in elderly patients represented high morbidity and mortality in critical ill and severely immune-compromised individuals. In these patients, poor prognosis is usually associated with advanced malignancies, increased use of invasive devices, prolonged mechanical ventilation and/or ICU stay, and long courses of broad-spectrum antibiotics. Antibiotic resistance rate is increasing, especially for trimethoprim-sulfamethoxazole and quinolones. Knowledge of local susceptibility patterns is helpful in determining which patients should receive appropriated empirical antibiotics against this pathogen. This study examined the data for *S. maltophilia* bacteremia in elderly patients, in an attempt to get better understanding of clinical characteristic and outcome.

Patients and method: A retrospective study was conducted at Thong Nhat hospital in the southern of Viet Nam. Patients who treated in the hospital with first positive blood culture between 1st January, 2018, and 31st December, 2019, were considered eligible for enrolment into this study. This investigation evaluated clinical characteristics, antibiotic resistances and outcome of patients as well as independent prognostic factors for mortality.

Results: Among 112 patients**,** average age was 77.4 ± 2, 0 years, 56.2% was male and SOFA score was 5.1 ± 4.2. Hypertension was common comorbid disease (59.8%). Nosocomial *S. maltophilia* bacteremia rate was 51.8%. Site of respiratory infection was 63.4%. The rate of septic shock accounted for 28.6%. Mortality rate of this population was high 30.4%. *S.maltophilia* was low resistant to TMP/SMX, moxifloxacin, levofloxacin, ciprofloxacin with the rate of 9.5%, 3.2%, 13.8%, 9.8%, respectively, as well as high resistant to meropenem (90.9%), imipenem (70%), gentamycin (88.8%), amikacin (75%). Multivariate analysis showed that the significant independent risk factors of mortality were SOFA score >7; mechanical ventilation and presentation with septic shock.

Conclusion: *Stenotrophomonas maltophilia* bacteremia is often severe in older patients. Mortality rate is still high and drug resistance is increasing. It is important to identify characteristic of antibiotic resistance to choose appropriate antibiotics as well as improve the patient's severity.

INTRODUCTION

Stenotrophomonas maltophilia is a multidrug-resistant gram-negative bacillus that is an opportunistic pathogen, particularly among hospitalized patients. It represents the fourth most common pathogen among nonfermenting gram-negative bacteria, with a reported incidence of 7.1 to 37.7 cases/10 000 discharges (regarding nosocomial infections) [1].

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Stenotrophomonas maltophilia bacteremia (SMB) is an important severe infection in older patients with the mortality rate of *S*MB is considerably high [2]. The 30-day mortality rates have been reported to range between 33% and 65.1% [3,4] and increases sharply if the patients receive inappropriate antimicrobial therapy (which mainly occurs empirically) [5]. Physicians therefore need to have a detailed knowledge of the clinical characteristics of such a fatal infection. Among patients with SMB, the proportion of elderly patients > 65 years is about 46% and mortality rate increases significantly [4]. Multi factors contributing to rate of death include

senescence of both human and cell-mediated immune systems; reduced physiologic reserve capacity; increased incidence of underlying illnesses; malnutrition; poor tolerance to invasive procedures; greater risk and incidence of nosocomial infections as well as higher rate of antibiotic resistant organisms [6.7]. Many prognostic factors for mortality, but almost study results are not consistent [4, 8, 9, 10, 11]. To our knowledge, no studies on SMB for elderly patients have been published in Viet Nam up to now. So, the data of severe *S. maltophilia* infections in the older patients had become an important issue. Thong Nhat hospital is 1200-bed tertiary geriatric hospital in the Southern of Viet Nam. This was a hospital of Ministry of Health with the function of treatment, teaching and scientific research. The hospital always overloaded with patients due to continued expansion of the geriatric population has been associated with an increase in the number of serious infections in older adults. Despite the great advances in medical science but SMB has still high mortality rate, so this study were to determine the clinical characteristic, antibiotic resistance, outcome and prognostic factors for mortality of SMB for evaluating epidemiology of pathogen and to treat appropriately.

MATERIALS AND METHODS

Study design and data collection

We conducted a retrospective study between 1st January, 2018, and 31st December, 2019, in Thong Nhat hospital. This was a largest geriatric university hospital of Ho Chi Minh City, Viet Nam. The university hospital is a 1200-bed tertiary care medical center. The source population consisted of all patients' ≥60 years of age and over who admitted to the hospital during the study period, and was diagnosed with first SMB with positive blood culture accumulated by the Microbiology Laboratory from the Department of Laboratory Medicine of Thong Nhat Hospital. For all eligible patients, the following data were collected: demographic characteristics, multiple organ failure SOFA, preexisting comorbid medical conditions, source of infection, initial vital signs, routine laboratory test results, admission and final discharge diagnoses, and identity of microorganisms isolated from the blood cultures. Anti-biogram was performed if blood culture was positive. Patient outcomes were defined as in hospital mortality or discharge from hospital. Mortality is defined as the periods from the onset of SMB to patient death. In-hospital mortality included patients who died during their initial admission.

Study definition

Bacteremia was defined as the isolation of gram negative or gram positive bacteria in a blood culture specimen. Clinically significant bacteremia was defined as at least one positive blood culture together with clinical features compatible with systemic inflammatory response syndrome, qSOFA (+) and SOFA ≥ 2.

Underlying diseases were defined as the medical diagnoses outlined in the individual medical file, based on the International Classification of Diseases-10 (ICD-10). Comorbid diseases included hypertension, diabetes, chronic cardiac failure, chronic coronary disease, chronic pulmonary disease, chronic hepatic disease, chronic renal disease and immune deficiency.

The source of the bacteremia was determined on the basis of the isolation of bacteria from the presumed portal of entry and clinical evaluation. The presence and source of a focal infection were classified by the final discharge diagnosis as lower respiratory tract infection, urinary tract infection, pancreacobiliary tract infection, bacterial peritonitis, skin and soft-tissue infection, vascular catheter-related infection. Those without a localized source of bacteria after an extensive admission workup were classified as primary bacteremia. Vascular catheter-related bacteremia was defined as the presence of a positive blood culture result from at least one peripheral blood sample, a catheter tip culture positive for an identical microorganism with identical anti-biogram, clinical signs of sepsis, and the absence of any other sources of sepsis

Nosocomial infection was defined as an infection that occurred >48h after hospital admission. Nosocomial bloodstream infections were defined according to the criteria proposed by the Centers for Disease Control and Prevention.

Septic shock was defined as sepsis associated with evidence of organ hypoperfusion and a systolic blood pressure < 90 or > 30 mm Hg less than the baseline or a requirement for the use of a vasopressor to maintain blood pressure and a serum lactate level greater than 2 mmol/L (18 mg/d) despite adequate volume resuscitation.

Organ failures assessed at emergency department admission and during hospitalization after SMB were characterized as follows: 1) acute renal failure, a serum creatinine level > 170 (μmol/L) or, in the case of preexisting renal dysfunction, a doubling of previous serum creatinine values, 2) acute hepatic failure, a bilirubin level > 20 mmol/l, 3) altered level of consciousness, a Glasgow Coma Scale score of <14 or a decrease in the score of at least 3 if a primary central nervous system injury was present, 4) acute respiratory distress, PaO2/FiO2 ≤ 400, and 5) hematological failure, platelets ≤ 150 (103/ml), 6) shock, arterial systolic blood pressure <90 mm Hg refractory to fluid repletion and requiring vasopressors to sustain a blood pressure of >90 mm Hg.

Statistical analysis

Statistical analysis was performed using SPSS Version 20.0. Descriptive statistics for categorical variables were performed by calculating frequencies and percentages. The variables were compared using the chi-square test or Fisher's exact test to observe the proportion differences. Binary univariate regression analysis was performed to identify factors associated with mortality. For evaluate independent predictors of in hospital mortality, multivariable Cox proportional hazards regression model was performed. All variables with p< 0.05 at univariate analysis were further analyzed in multivariate binary regression. The strength of the association between prognostic variables and the outcome of interest was expressed as Odd ratio, and their corresponding 95% confidence intervals were calculated. P-value < 0.05 was considered statistically significant. Only the first episode of SMB was considered for the analysis.

Interpretation of the antimicrobial susceptibility results was carried out in accordance with CLSI 2018 guidelines [12]. Antimicrobial sensitivity results were expressed in terms of sensitivity rates according to the CLSI M39 guidelines [13]. To avoid the effect of repetitive isolation of strains on antimicrobial sensitivity, the first isolation of strains from the

same site of infection in a patient was analyzed according to CLSI M39 guidelines.

Ethical approval

Ethical approval for the study were obtained from ethical committee of Nguyen Tat Thanh university. Permission to conduct the study at Thong Nhat hospital was granted by executive director and ethical committee of hospital because the study was retrospective and they were no direct contact with patients.

RESULTS

Patient characteristics and comorbidity

Characteristics of patients with SMB are listed in Table 1.
112 patients aged 60 and older (mean 77.4, median 1.4) were identified; 63 patients were male (56.2%); SOFA score was 5.1±1.4. 54 (48.2%) of patients were community acquired. The remaining 58 (51.8%) were nosocomial. Septic shock accounted for 32 patients (28.6%). Patients with higher rates of renal failure (60.7%), hematological failure (50.9%), cardiovascular failure (56.3%) and respiratory failure (50%) compared with other organs. The number of patients treated in medical ward, surgical ward and ICU were 42%, 10.7%, 47.3%, respectively. The most common medical comorbidities included hypertension (59.8%), diabetes mellitus (33.9%), chronic cardiac failure (36.6%), and chronic renal disease (32.5%).

Table 1. Characteristics, clinical features, site of infection of SMB

Variable	N(% of 112)
Sex	
Male	63 (56.2)
Female	49 (43.8)
Age, years, (IQR)	77.4 (1.4)
SOFA score (mean ± SD)	5.1 ± 4.2
Multi-organ failure	
Cardiovascular	63 (56.3)
Respiratory	56 (50)
Hepatic	18 (16.1)
Renal	68 (60.7)
Hematologic	57 (50.9)
Neurologic	44 (39.3)
Accquisition	
Community	54 (48.2)
Nosocomial	58 (51.8)
Septic shock	32 (28.6)
Mechanical ventilation	51 (55.5)
Ward of admission	
Medical	47 (42)
Surgical	12 (10.7)
ICU	53 (47.3)
Underlying disease	
Hypertension	67 (59.8)
Diabetes	38 (33.9)
Coronary disease	26 (23.5)
Cardiac failure	41 (36.6)
Hepatic disease	6 (5.4)
Kidney disease	36 (32.5)
Immune Deficiency	7 (6.3)
Chronic lung disease	8 (7.1)
Primary site of infection	
Catheter related	4 (3.6)
Pancreacobiliary tract	3 (2.7)
Urinary tract	11 (9.8)
Lung	71 (63.4)
Peritoneum	7 (6.3)
Skin	6 (5.4)
Unknown	10 (8.9)

IQR, interquartile range; SOFA score, sequential organ failure assessment score
ICU, Intensive care unit; SD, Standard deviation

Related to the primary source of infection, respiratory infection was most common (63.4%), followed by urinary tract (9.8%). Pancreaticobiliary tract, vascular catheter related infection, skin and soft tissue, peritoneum accounted for the low percentage (2.7%), (3.6%), (5.4%), (6.3%), respectively. Site of infection was not observed with the rate (8.9%)

Antibiotic resistance of S. maltophilia

The antibiotic resistance patterns of the isolate were shown in Table 2. Resistant rate of *S. maltophilia* is high to carbapenem 69.9-90.9%, third generation cephalosporin 3 > 83%, nhóm aminoglycoside 75-88%, colisstin 50.5%, Especially, bacillus is low resistant to trimethoprim/ sulfamethoxazole (TMP/SMX) 9.5%, quinolones 3.2-13.8%, tigecyclin 6.8% and fosfomycin 3%

Table 2: Percentage antimicrobial resistance of *Stenotrophomonas maltophilia*

	S. maltophilia (% of 112)
Meropenem	90.9
Imipenem	69.9
Ertapenem	6.7
Levofloxacin	13.8
Ciprofloxacin	9.8
Moxifloxacin	3.2
Colistin	50.5
Tigecyclin	6.8
Gentamycin	88.8
Amikacin	75.0
Cefepim	83.7
Cefotaxim	97.2
Piperacillin	86.5
Ceftazidim	87.9
Fosfomycin	3.0
TMP/SMX	9.5
Tobramycin	96.7
Aztreonam	100

TMP/SMX, Trimethoprim/Sulfamethoxazole

In hospital mortality rate and predictors

Table 3 showed the patient characteristics of hospital survivors (n=78) and nonsurvivors (n=34). In hospital mortality rate of all patients was 30.4%.

Univariable analysis (Table 3) revealed that SOFA score, presentation of septic shock, ICU care, mechanical ventilation were significantly associated with mortality, with p <0,001.

Table 3: Risk factors for mortality based on univariable analysis.

Characteristic	Value for group(a)		OR(95%CI)	P Value
	N0 of Survivors n= 78(%)	N0 of Nonsurvivors n= 34(%)		
N0. of males	45(57.69%)	18(52.94%)	1.21 (0.54 – 2.72)	0.397
Age >75	43 (55.13)	24 (70.59)	1.95 (0.83-4.63)	0.092
SOFA >7	5 (6.41)	24 (70.59)	35.04 (10.89-112.72)	<0.001
Underlying disease				
Hypertension	47 (60.26)	20 (58.82)	0.94 (0.42-2.12)	0.525
Diabete	26 (33.33)	12 (35.29)	1.09 (0.47-2.54)	0.502
Coronary disease	20 (25.64)	6 (17.65)	0.62 (0.23-1,72)	0.252
Cardiac failure	29 (37.18)	12 (35.29)	0.92 (0.40-2.14)	0.512
Hepatic disease	3 (3.85)	3 (8.82)	2.42 (0.46-12.65)	0.258
Kidney disease	27 (34.62)	9 (26.47)	0.68 (0.28-1.66)	0.267
End-stage renal disease	3 (3.85)	1 (2.94)	0.76 (0.08-7.56)	0.646
Immune Deficiency	5 (6.41)	2 (5.88)	0.91 (0.17-4.95)	0.641
Chronic lung disease	6 (7.69)	2 (5.88)	0.75 (0.14-3.92)	0.541
Comorbid condition				
Septic Shock	7 (8.97)	25 (73.53)	28.18 (9.49-83.62)	<0.001
ICU care	25 (32.05)	28 (82.35)	9.89 (3.63-26.94)	<0.001
Ventilation	21 (26.92)	30 (88.24)	20.36 (6.40-64.75)	<0.001
Primary site of infection				
Catheter related	4 (5.13)	0 (0)	0.95 (0.90-1.00)	0.230
Pancreacobiliary tract	2 (2.56)	1 (2.94)	1.15 (0.10-13.15)	0.666
Urinary tract	9 (11.54)	2 (5.88)	0.48 (0.10-2.35)	0.291
Lung	46 (58.97)	26 (76.47)	2.38 (0.96-5.93)	0.044
Peritoneum	5 (6.41)	2 (5.88)	0.91 (0.17-4.95)	0.641
Skin	4 (5.13)	2 (5.88)	1.16 (0.20-6.64)	0.593
Neurology	0 (0)	0 (0)		
Unknown	9 (11.54)	1 (2.94)	0,23 (0.03-1.91)	0.132
Nosocomial	36 (46.15)	22 (64.71)	2.14 (0.93-4.92)	0.054

χ^2 tests.

(a) Number and percentage (in parentheses) of patients with each characteristic are shown.

In Table 4, SOFA score >7 (6.9, 1.35-36.18, p=0.021); presence of septic shock (5.0, 1.00-25.05, p=0.05), mechanical

ventilation (20.8, 1.46-296.32, p=0.025), were identified as major independent predictors of mortality following multivariate Cox regression. In this analysis, ICU care did not reach the level of significance.

Table 4. Independent risk factors for mortality in SMB based on multivariate analysis.

Risk factors	OR (95% CI)	P value
SOFA score >7	6.9 (1.35-36.18)	0.021
Septic shock	5.0 (1.00-25.05)	0.050
Mechanical ventilation	20.8 (1.46-296.32)	0.025

DISCUSSION

This study was undertaken to evaluate the clinical characteristic, antibiotic resistance, outcome as well as risk factors for mortality of SMB in elderly patients. We only investigated in the elderly because this patient population was very frail. Older patients with SMB often had a poor prognosis due to frequent co-morbidities, declining functional status, altered immune function, long-term institutionalization, malnutrition, greater risk of nosocomial infection, poor tolerance of invasive procedures, poor response to antimicrobial therapy, higher rates of adverse reactions to drugs, including antibiotics. This could explain why this population segment was particularly susceptible to bacterial infections. In our knowledge, the current study is the largest study for SMB in elderly patient in Viet Nam. In Table 1, average age was 77.4 year and mortality rate accounted for 30.4%. We identified that age wasn't an independent factor for mortality in this study. This result was also noted in the study of other authors [9, 10, and 11].

It has been reported that the severity of illness is associated with poor outcome among patients with *S*MB which was corroborated by the results of the present study. Patients with bacteremia were significantly more likely to have more severe illnesses as determined by APACHE II score and SOFA score. Acute physiology and chronic health evaluation II (APACHE II) and sepsis related organ failure assessment (SOFA) scores were significantly higher in nonsurvivors [14]. Several studies have reported similar results, as well as reporting that patient medical conditions were more important factors associated with mortality than the appropriateness of antibiotics [14,15[. Garcia Paez showed that patients with APACHE II score >20 and SOFA score >10 had a survival chance of, respectively, less than 8% and less than 10% ($p \leq 0.001$) at 21 days after the first positive *S. maltophilia* culture [12]. SOFA score > 4 [16, 17] or SOFA score > 6 [18] were factors significantly associated with death. Our study identified that SOFA score > 7 was an independent risk factors associated with mortality. That showed serious condition of our patients.

The rate of septic shock in this investigation was 28.6% with mortality rate of 78% (table 2). In several large studies, septic shock was present in 38.5% with mortality rate reaching 70% (19). These patients usually died in the context of multiple organ failure. The presence of septic shock was independently associated with in-hospital mortality in multivariable analysis of our research. This result of study is similar to result of some other authors [3, 19, and 20].

In our study, it was noted that community SMB rate accounted for (48.2%), and nosocomial SMB rate (51.8%). The patients may facilitate the acquisition of exogenous bacteria and invasive procedures which are increasingly being performed in old people, may compromise the natural barriers of innate immunity and created a portal of entry for nosocomial bacteremia, especially from respiratory tract. In this site our study, respiratory infection rate accounted for 63.4%, mortality group had higher rate of respiratory infection than death group. Certain patients had infection of lower respiratory tract occurring on chronic respiratory disease such as chronic obstructive pulmonary disease, pulmonary fibrosis. Mechanical ventilation was in the case of acute respiratory failure and patients were often severe. Several physiologic changes in older adults have been implicated as risk factors for lower respiratory tract. Changes in basic lung physiology as a result of aging include decreased elastic recoil, increased air trapping (senile emphysema), decreased chest wall compliance and reduced respiratory muscle strength. These factors may act to increase baseline work of breathing, giving older individuals less reserve to cope with bacterial infections in the lung. In addition, reduced mucocilliary clearance and diminished cough reflex have been described [21]. Therefore mechanical ventilation is independent factor for mortality noted in this research. Other factors for mortality were showed in certain studies but not evaluated in our study: charlson index, indwelling of a central venous catheter [4], hypoalbuminemia, hematologic malignancy, quinolone-resistant strains [11].

S. maltophilia is a multidrug-resistant organism, therefore antibiotic options are limited and clinical data are limited regarding optimal therapy. Treatment of *S. maltophilia* infections has always been challenging because of its intrinsic resistance to most antimicrobial agents, especially carbapenem. TMP/ SMX remain the most effective antimicrobial agent against *S. maltophilia* and the recommended first-line agent [22, 23]. We identified resistant rate to carbapenem in 69-90.9%, third generation cephalosporin >83%, aminoglycoside 75-88%, colistin 50.5%, Especially, pathogens were low resistant to TMP/SMX 9.5%, quinolones 3.2-13.8% and fosfomycin 3%

In a worldwide study which comprised 1586 *S. maltophilia* strains, the highest resistance rate to trimethoprim/sulfamethoxazole (TMP/SMX) was 9.2% in Asian-Pacific region, compared with the lowest (1.1%) in Europe [24]. Resistance rate of 9.5% to TMP/SMX was observed in our study. Still, treatment for *S. maltophilia* infection with TMP/SMX may not be possible due to resistance, allergies, toxicities, or drug shortages [25]. Therefore, newer agents like ticarcillin/clavulanic, new fluoroquinolones (such as moxifloxacin and levofloxacin), tetracyclines (such as minocycline and tigecycline) have been proposed as promising alternative agents [26]. A recent survey evaluated the efficacy of levofloxacin in the treatment of *S. maltophilia* bacteremia. Results showed that patients receiving levofloxacin showed clinical outcomes similar to those receiving TMP-SMX but suffered less adverse events [27]. Similar conclusion was drawn in another research by Wang *et al*. [28]. According to our study, levofloxacin was most common agent used in combination therapy, while TMP/SMX was rarely used in clinical practice.

A novel agent tigecycline is gradually being administrated against *S. maltophilia* infections for its good in vitro activity (94.5%-96.5%) [24]. However, tigecycline has great bio-distribution after intravenous injection, leading to lower serum drug levels. Is this obstructive of using tigecycline against bacteremia? Wu and Shao administrated tigecycline at the dose of 100 mg every 12 hours to treat a female patient who was

diagnosed with AML and confirmed *S. maltophilia* bacteremia under bone marrow suppression. Finally, the patient recovered from persistent fever and the CT scan of the chest turned normal [29]. We may conclude that the approved dosage of tigecycline might not be sufficient for bacteremia due to its low blood concentration and increasing the dosage could help. While Falagas *et al*. concerned that safety of high-dose tigecycline was still uncertain for its dose-dependent adverse effects [30]. And it needs to be noted that, in a recent study, no significant differences were found for mortality and clinical response rates between TMP/SMX and tigecycline treatment in *S. maltophilia* infections [31]. In conclusion, tigecycline might be considered an alternative for patients who are unable to tolerate TMP/SMX and the dose should be individualized. We showed that resistance was low to tigecyclin (6.8%). therefore, this antibiotic was selected for treatment.

Colistin has proven to be active against *S. maltophilia in vitro* and effective for the treatment of patients in combination with other drugs. However, an increased incidence of colistin-resistant isolates has also been observed in recent years [32]. colistin resistance may arise through several mechanisms such as regulated modifications of the LPS molecule, mutations in genes involved in LPS synthesis or variations in global gene expression induced by environmental changes such as variations in pH or cations or the presence of cationic antimicrobial polypeptides, heteroresistance and biofilm formation have accelerated the emergence of colistin resistance. We rarely use colistin in clinical practice because resistant rate was still high.

Fosfomycin presents good activity against multidrug resistant gram-negative bacteria. The resistances seem to increase in settings with a high use of fosfomycin and along with exposure when faced with multidrug-resistant pathogens [33]. *S. maltophilia* has high rates of resistance, either through intrinsic or acquired mechanisms to aminoglycosides, fosfomycin. *S. maltophilia* are not susceptible to fosfomycin was noted in Falagas' study [34]. Our study showed that low resistant rate of fosfomycin in vitro in 3%. Therefore, drug choice in combination therapy may be considered. We didn't use this antibiotic for treatment.

There are several limitations of this study that should be acknowledged. First, we performed a retrospective study, therefore some other pertinent information were not recorded. Second, it is a single center study which limits its external validity. Third, there was a relative small study sample, which can also influence its generalizability. Nevertheless, the sample size was large enough to demonstrate significant differences, so there was enough study power.

In conclusion, the current study showed that mortality of SMB was still high despite relatively low resistance to TMX/SMX and quinolones. SOFA score, septic shock, mechanical ventilation were independent factors for mortality. It was important to identify causative pathogen as well as antibiotic resistance to choose an appropriate treatment.

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How to cite this article:

Hoang Van Quang *et al* (2021) 'Stenotrophomonas Matophilia Bacteremia In Elderly Patients In The Southern of Vietnam: Patient Characteristic, Antibiotics Resistance And Treatment Outcome', *International Journal of Current Advanced Research,* 10(02), pp. 23877-23882. DOI: http://dx.doi.org/10.24327/ijcar.2021.23882.4731

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