

Clinico-epidemiological Analysis of *Stenotrophomonas maltophilia* Bacteraemia, its Associated Risk Factors and Outcome in Patients Admitted at a Tertiary Care Centre in Northern India- A Retrospective Cohort Study

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ABSTRACT

Introduction: *Stenotrophomonas maltophilia* is a Gram-negative, motile, and glucose non fermenting bacterium commonly found in hospital settings. It poses a significant risk to immunocompromised individuals, often causing nosocomial infections.

Aim: To identify the risk factors associated with *Stenotrophomonas maltophilia* bacteraemia and compare the factors influencing patient survival and mortality.

Materials and Methods: Clinical and laboratory data from 39 cases of *Stenotrophomonas* bacteraemia encountered between July 2021 and July 2022 in the Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, were analysed in the present retrospective study in August 2022. The study included all cultures positive for *S. maltophilia* bacteraemia, identified through Matrix-assisted Laser Desorption Ionisation Time-Of-Flight Mass Spectrometry (MALDI-TOF-MS). Antibiotic susceptibility testing was performed using the Kirby-Bauer disk diffusion method, following the Clinical and Laboratory

Standards Institute (CLSI) guidelines. Statistical analysis and outcome assessment were conducted using Statistical Package for Social Sciences (SPSS) version 20.0.

Results: Clinical data from all 39 bacteraemia patients were extracted from the hospital information system for analysis. The mean age of the patients included in the present study was 46.0±20.29 years, with a male predominance of 27 (69.23%). The most common risk factors associated with *S. maltophilia* bacteraemia were the presence of an indwelling catheter in 21/39 cases (53.8%) and co-existing pulmonary infections in 18/39 cases (46.2%). *S. maltophilia* isolates exhibited high susceptibility to Minocycline (94.87%), Ticarcillin-Clavulanic acid (87.18%), Levofloxacin (84.62%), and Cotrimoxazole (84.62%). The 30-day mortality rate was reported as 28.20% (11/39).

Conclusion: *S. maltophilia* can cause various infections in immunocompromised patients. The appropriate use of empirical antibiotics and strict adherence to infection control measures can reduce hospital stays, as well as 14-day and 30-day mortality rates among affected patients.

Keywords: Empirical antibiotics, Immunocompromised patient, Indwelling catheters, Infection control measures, Nosocomial

INTRODUCTION

Stenotrophomonas maltophilia is a Gram-negative, motile, and glucose non fermenting bacterium that is commonly found in the hospital environment [1,2]. The recent increase in bacteraemia cases caused by *S. maltophilia* in various hospital wards has prompted further evaluation of this microorganism. It has the ability to colonise medical devices and the respiratory tract's epithelial cells [2]. *S. maltophilia* is recognised as a significant pathogen in nosocomial infections, particularly affecting immunocompromised individuals [3-5]. Several cases of *S. maltophilia* infections have been reported in patients with haematological malignancies [6-8]. While pneumonia and bacteraemia are the most common manifestations, *S. maltophilia* infections have also been reported in wounds, intraabdominal organs, and the urinary tract [2,9,10].

S. maltophilia bacteraemia is identified in patients exhibiting clinical symptoms of sepsis, with one or more blood cultures showing growth of the microorganism [1]. Nosocomial infection is acknowledged if a blood culture is positive after ≥48 hours of admission. Community-acquired bacteraemia is considered when bacteraemia is present on admission or occurs within 48 hours of admission in patients who do not meet the criteria for nosocomial bacteraemia [9]. The delay in initiating appropriate antibiotic therapy is often attributed to

the challenge of distinguishing between colonisation and infection. Treatment of these isolates is complicated due to multidrug resistance and intrinsic resistance to various drugs. Trimethoprim-Sulfamethoxazole (TMP-SMX) is the preferred drug of choice for treating *S. maltophilia* infections [11], although fluoroquinolones and minocycline are also considered as management options [11,12].

While previous studies have explored the diagnostic and demographic characteristics [13,14], risk factors, and clinical presentation of *Stenotrophomonas* bacteraemia [15-17], few studies in Indian literature have compared the risk factors associated with death and survival in patients with *Stenotrophomonas maltophilia* infections. Therefore, the present study aims to examine cases of *S. maltophilia* bacteraemia, including underlying co-morbidities and risk factors that predispose patients to adverse outcomes. The main objective is to analyse the demographic and clinical characteristics of *Stenotrophomonas maltophilia* bacteraemia, and the associated risk factors and outcomes in patients.

The objectives of the present study were to study the antibiotic susceptibility pattern of *S. maltophilia* isolates obtained from bloodstream infections and to compare the demographic and risk factors between the group of patients who survived and died, and assess mortality and survival rates.

MATERIALS AND METHODS

The present retrospective cohort study was conducted in the Department of Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. Clinical and laboratory data from 39 cases of *Stenotrophomonas* bacteraemia encountered between July 2021 and July 2022 were obtained from the hospital information system and analysed in August 2022. The study protocol was approved by the Institutional Ethics Committee, and informed consent was waived due to the retrospective nature of the study.

The sample size was determined by including all *S. maltophilia* isolates obtained from patients with bloodstream infections during the study period.

Inclusion criteria: *S. maltophilia* isolates obtained from patients with clinical symptoms of sepsis and one or more blood cultures showing growth of the microorganism were included in the study.

Exclusion criteria: Isolates collected from a single positive culture without any significant clinical parameters were considered contaminants and excluded from the study.

Study Procedure

The 39 cases were divided into two groups based on the outcome of the patients in terms of survival. The first group included 28 (71.79%) patients who survived, while the second group included 11 (28.20%) patients who died. Significant risk factors leading to death in patients with *S. maltophilia* bacteremia were evaluated. The evaluations were supported by a 120-day Kaplan-Meier survival analysis with respect to underlying comorbidities. Demographic characteristics such as age, gender, length of hospitalisation, etc., and clinical characteristics like underlying co-morbidities and risk factors, as well as diagnostic parameters like the total leukocyte count and procalcitonin assay, were extracted from the hospital information system. Blood cultures were processed in the Bacteriology section of the Department of Microbiology using the automated BACTEC blood culture system. The cultures showing growth of *Stenotrophomonas maltophilia* were identified by phenotypic biochemical reactions [18] and confirmed by MALDI-TOF-MS. Only the first episode of bacteraemia was included for analysis to avoid duplication.

Drug susceptibility testing was performed using the Kirby-Bauer disk diffusion and Epsilometric-test strip (E-test) methods, following the CLSI guidelines [19]. A specific panel of antibiotics suggested for *S. maltophilia* was used on cation-adjusted Muller Hinton agar plates [20].

Empirical antibiotic administration refers to the initiation of antibiotics routinely administered in the ward for a specific ailment before performing Antimicrobial Susceptibility Testing (AST) on the specific microorganism. The most common broad-spectrum antibiotics administered empirically in most wards of the hospital were intravenous meropenem at 500 mg every 8 hours for five days and intravenous teicoplanin at 400 mg every 12 hours for three days, followed by 400 mg once a day for two days.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS version 20.0 software. Continuous variables, which include the age of patients, length of hospitalisation, time of isolation of the microorganism, procalcitonin level, and total leukocyte count, were expressed as mean±standard deviation. Survival analysis was conducted to assess the 14-day and 30-day mortality rates. Categorical variables, including gender, underlying co-morbidities, risk factors, antibiotic exposure, incidence of Intensive Care Unit (ICU) stay in patients with *S. maltophilia* bacteraemia, and distribution of *S. maltophilia* bloodstream infection from various wards, were compared using the

two-tailed Chi-square test. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 39 blood samples in BACTEC blood culture bottles were included in the study, which flagged positive and yielded growth of *S. maltophilia*. The distribution of the cases of *Stenotrophomonas maltophilia* bacteraemia from various departments is shown in [Table/Fig-1], with the highest number of cases obtained from the haematology and gastroenterology departments, followed by the surgical gastroenterology and nephrology departments.

Departments where incidence of <i>Stenotrophomonas</i> bacteraemia was noted	n (%)
Anaesthesia	2 (5.13%)
Cardiology	1 (2.56%)
CCM	2 (5.13%)
CVTS	1 (2.56%)
Emergency	3 (7.69%)
Endocrine surgery	1 (2.56%)
Gastroenterology	5 (12.82%)
Haematology	5 (12.82%)
Hepatology	3 (7.69%)
Nephrology	6 (15.38%)
Neurology	1 (2.56%)
Paediatric gastroenterology	3 (7.69%)
Pulmonary medicine	2 (5.13%)
Surgical gastroenterology	4 (10.26%)

[Table/Fig-1]: Departments from which incidence of *Stenotrophomonas maltophilia* bacteraemia were reported at our hospital (N=39).
CCM: Critical care medicine; CVTS: Cardiovascular thoracic surgery

The demographic parameters and associated risk factors of the *Stenotrophomonas maltophilia* bacteraemia patients are presented in [Table/Fig-2]. The mean age of the patients included in the study was 46.0±20.29 years, with a male predominance (69.23%). Most of the episodes of bacteraemia (37/39) were nosocomial, and the most common sources of bacteraemia were pulmonary infections (46.2%) and central venous catheters (53.8%). The median length of hospital stay among these patients was 26.0±19.08 days, and the mean time of isolation of the microorganisms from blood samples was 9.0±8.71 days. The 30-day mortality rate was reported as 28.20%.

Characteristics	n (%)
Age (years); mean±SD (range)	46.0±20.29 (1-74)
Male gender	27 (69.23%)
Co-morbidities	
Cardiovascular disease	2 (5.1%)
Central venous catheters	21 (53.8%)
Solid tumour	3 (7.7%)
Diabetes mellitus	4 (10.3%)
Haematologic malignancy	5 (12.8%)
Pulmonary infections	18 (46.2%)
Mechanical ventilation/Intubation	5 (12.8%)
Nervous system diseases	1 (2.6%)
Severe acute pancreatitis	1 (2.6%)
Chronic kidney disease	11 (28.2%)
Dialysis	6 (15.4%)
Immunosuppression	17 (43.6%)
Overall hospital stay, mean±SD (range)	26.0±19.08 (4-119)
Time of isolation of microorganism from sample, mean±SD (range)	9.0±8.71 (1-42)
ICU residence	5 (12.8%)

Distribution of infection	
Surgery wards	9 (23.1%)
ICU	5 (12.8%)
Medicine wards	25 (64.1%)

[Table/Fig-2]: Overall demographic parameters and associated risk factors of *Stenotrophomonas maltophilia* bacteraemia patients (N=39). Overall hospital stay in days; Time of isolation of microorganism from sample in days; *SD: Standard deviation; ICU: Intensive care unit

[Table/Fig-3] shows that 53.85% of the cases were on appropriate empirical antibiotics, while 46.15% were not. The use of carbapenems as empirical antibiotic treatment was significantly higher in those not receiving appropriate empirical antibiotics. Fluoroquinolones and cotrimoxazole were significantly more commonly used in those receiving appropriate empirical antibiotics. The length of antibiotic therapy was comparable between the two groups.

Parameters	<i>S.maltophilia</i> bacteraemia patients receiving appropriate empirical antibiotics (N=21)	<i>S.maltophilia</i> bacteraemia patients not receiving appropriate empirical antibiotics (N=18)	p-value*
Demographics			
Age in years, mean±SD (range)	42.19±22.24 (1-74)	46.61±18.09 (8-73)	0.505
Male sex	14 (66.67%)	13 (72.22%)	0.708
Underlying co-morbidities			
Immunocompromised status	9 (42.86%)	8 (44.44%)	0.921
Diabetes mellitus	2 (9.52%)	2 (11.11%)	0.871
Chronic kidney disease	6 (28.57%)	5 (27.78%)	0.956
Pulmonary infections	12 (57.14%)	6 (33.33%)	0.137
Previous exposure to antibiotics			
Carbapenems	0	9 (50%)	<0.001*
Cephalosporins	5 (23.81%)	5 (27.78%)	0.777
Fluoroquinolones	5 (23.81%)	0	0.027*
Tetracycline	3 (14.28%)	1 (5.56%)	0.370
Aminoglycosides	0 (0.0%)	2 (11.11%)	0.117
Cotrimoxazole	8 (38.09%)	1 (5.56%)	0.016*
Clinical characteristics			
Length of hospital stay, mean±SD (range)	23.94±12.88 (10-54)	30.67±22.99 (4-119)	0.258
Invasive medical devices			
Mechanical ventilator	4 (19.05%)	1 (5.56%)	0.209
Intravascular device	9 (42.86%)	12 (66.67%)	0.137

[Table/Fig-3]: Characteristics of *Stenotrophomonas maltophilia* bacteraemia patients and comparison of features among patients receiving and not receiving appropriate empirical antibiotics (N=39). Length of hospital stay in days; Chi-square test; *p-value ≤0.05 is statistically significant; SD: Standard deviation

The antibiotic susceptibility pattern of the *Stenotrophomonas maltophilia* isolates is presented in [Table/Fig-4]. Minocycline, ticarcillin-clavulanic acid, levofloxacin, and cotrimoxazole showed the highest susceptibility against the isolates, while ceftazidime and chloramphenicol had lower sensitivity.

Antibiotics used for susceptibility testing	Susceptible	Intermediate	Resistant
Ceftazidime	26 (66.67%)	1 (2.56%)	12 (30.77%)
Chloramphenicol	25 (64.10%)	1 (2.56%)	13 (33.33%)
Cotrimoxazole	33 (84.62%)	0	6 (15.38%)
Levofloxacin	33 (84.62%)	2 (5.13%)	4 (10.26%)
Minocycline	37 (94.87%)	2 (5.13%)	0
Ticarcillin-clavulanic acid	34 (87.18%)	0	5 (12.82%)

[Table/Fig-4]: Antibiotic sensitivity pattern of *Stenotrophomonas maltophilia* isolates from blood samples (N=39).

The clinical outcomes, including 14-day and 30-day mortality, and non-clinical outcomes, such as the length of hospitalisation, are shown in [Table/Fig-5]. The 30-day mortality was significantly higher in those not receiving appropriate empirical antibiotics. The length of hospital stay was longer in cases receiving inappropriate empirical antibiotics. However, the cost of hospitalisation was comparable between the two groups.

Outcomes	<i>S.maltophilia</i> bacteraemia patients who received appropriate empirical antibiotic(s) (n=21)	<i>S.maltophilia</i> bacteraemia patients who did not receive appropriate empirical antibiotic(s) (n=18)	p-value*
Clinical outcomes			
Mortality			
14-day	2 (9.52%)	2 (11.11%)	0.871
30-day	0	7 (38.89%)	0.002*
Non-clinical outcomes			
Length of hospital stay, mean±SD (range)	23.94±12.88 (10-54)	30.67±22.99 (4-119)	0.258

[Table/Fig-5]: Comparison of outcomes between patients with *S.maltophilia* bacteremia who did or did not receive appropriate empirical antibiotic(s) (N=39). Length of hospital stay in days; Chi-square test; *p-value ≤0.05 is statistically significant; SD: Standard deviation

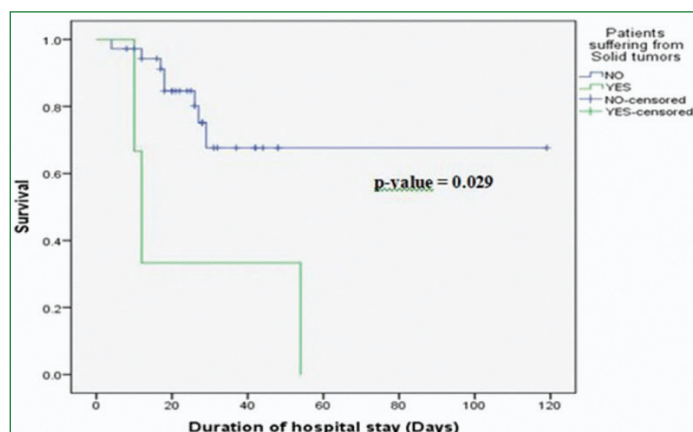
The risk factors related to 30-day mortality of *Stenotrophomonas maltophilia* bacteraemia patients are listed in [Table/Fig-6]. Chemotherapy was identified as a statistically significant risk factor among those who died. Procalcitonin levels were significantly higher in patients who succumbed to their infections.

Parameters	Total (N=39)	Survived (n=28)	Died (n=11)	p-value
Age				
>65 years	6 (15.38%)	4 (14.29%)	2 (18.18%)	0.762
≤65 years	33 (84.62%)	24 (85.71%)	9 (81.81%)	0.762
Gender				
Male	27 (69.23%)	18 (64.28%)	9 (81.81%)	0.286
Female	12 (30.77%)	10 (35.71%)	2 (18.18%)	0.286
Risk factors for <i>Stenotrophomonas maltophilia</i> bacteraemia				
Central venous catheter	21 (53.85%)	13 (46.43%)	8 (72.73%)	0.138
Mechanical ventilation/Intubation	5 (12.8%)	4 (14.29%)	1 (9.09%)	0.662
Chemotherapy	3 (7.69%)	0 (0.0%)	3 (27.27%)	0.004*
Haemodialysis	6 (15.38%)	4 (14.29%)	2 (18.18%)	0.762
Immunosuppression	17 (43.59%)	12 (42.86%)	5 (45.45%)	0.883
Organ transplant	1 (2.56%)	1 (3.57%)	0 (0.0%)	0.525
ICU residence	5 (12.8%)	4 (14.29%)	1 (9.09%)	0.662
Blood transfusion	5 (12.8%)	3 (10.71%)	2 (18.18%)	0.530
Pulmonary infections	18 (46.15%)	15 (53.57%)	3 (27.27%)	0.138
Diabetes mellitus	4 (10.26%)	3 (10.71%)	1 (9.09%)	0.880
Chronic kidney disease	11 (28.20%)	8 (28.57%)	3 (27.27%)	0.935
Other parameters				
Length of hospital stay, mean±SD (range)	44.23±20.29 (1-74)	42.46±22.32 (1-74)	48.73±13.73 (32-72)	0.392
Procalcitonin (normal range <0.5 IU) mean±SD	3.94±5.90	0.66±0.80	12.28±4.90	<0.001*
Leukocytes (normal range 4,000-10,000/μL) mean±SD	15729.28±6346.74	15081.36±6243.11	17378.55±6607.90	0.315

[Table/Fig-6]: Risk factors related to 30-day mortality of *Stenotrophomonas maltophilia* bacteraemia patients (N=39). Length of hospital stay in days; Chi-square test; *p-value ≤0.05 is statistically significant; SD: Standard deviation

According to the Kaplan-Meier survival analysis, the absence of solid tumours was significantly associated with a higher 120-day survival rate, as shown in [Table/Fig-7]. Further, multivariate Cox regression

analysis showed that pulmonary infections and solid tumours were significant risk factors associated with the 120-day survival rate in *Stenotrophomonas maltophilia* bacteraemia patients.



[Table/Fig-7]: A total of 120-day survival in patients with *Stenotrophomonas maltophilia* bacteraemia in association with patients suffering from solid tumours (N=39).

DISCUSSION

Over the past decade, *Stenotrophomonas maltophilia* has secured its position as the third most prevalent non-lactose fermenting, Gram-negative bacteria, capable of causing nosocomial infections following *Pseudomonas aeruginosa* and *Acinetobacter* species [1]. In this retrospective study, 39 cases of *Stenotrophomonas maltophilia* bacteraemia were evaluated from July 2021 to July 2022 at a teaching hospital in Northern India.

The majority of patients in this study were suffering from more than one comorbid condition and disease. The mortality rate observed at our hospital due to *Stenotrophomonas maltophilia* bacteraemia was 28.20% (11/39), which is comparable to studies conducted by Falagas ME et al., Garcia Paez JI et al., Garazi M et al., and Kanchanasuwan S et al., [7,9,21,22]. Several studies have reported that patients admitted to ICUs were more susceptible to infections caused by *Stenotrophomonas maltophilia*, which is in contrast to our study where only 5/39 (12.8%) patients were admitted to the ICU, and the maximum number of patients were admitted to the medicine wards, amounting to about 25/39 (64.1%) [4-6,8,9,23,24].

The most common risk factors among the patients included in this study were pulmonary infections, accounting for 18/39 (46.15%), but only 5/39 (12.8%) needed mechanical ventilation. Although a study by Alonso A and Martinez JL accounts for mechanical ventilation being a risk factor in the acquisition of *Stenotrophomonas maltophilia* bacteraemia [24], central venous catheters (21/39, 53.8%) accounted for the most common risk factors in this study, suggesting the microorganism's ability to colonise the indwelling catheters, in agreement with a study by Umar Z et al., [25]. The value of Procalcitonin was significantly higher in patients who succumbed to their infections and was an avid marker for the diagnosis of sepsis, corroborating with the findings of Wang L et al., and Garner JS et al., [26,27].

The use of inappropriate empirical antibiotics can be a risk factor for developing an infection with **Stenotrophomonas maltophilia**. Most of the patients admitted to the hospital were treated for various infections using Carbapenems (9/39, 23.08%). Since **Stenotrophomonas maltophilia** isolates are intrinsically resistant to Carbapenems, the widespread use of Carbapenems can lead to an outbreak of nosocomially acquired *Stenotrophomonas maltophilia* infections due to the selection of Carbapenem-resistant isolates. The antibiotic sensitivity pattern of the *Stenotrophomonas maltophilia* isolates described rising resistance to commonly used antimicrobial agents like Cephalosporins. In this study, Ceftazidime mostly represents the group, and resistance of 30.77% (12/39) was observed, which corresponds with studies conducted by Alonso A et al., and Zhang L et al., [24,28]. The resistance rates for

drugs like Minocycline (0.0%), Ticarcillin-clavulanic acid (12.82%), Cotrimoxazole (15.38%), and Levofloxacin (10.26%) were relatively low in comparison to regularly used antibiotics. Thus, the most commonly used first-line antibiotics against the microorganism were Levofloxacin and Cotrimoxazole, and in cases of resistance to these antibiotics, Minocycline and Ticarcillin-clavulanic acid were employed.

The data from this study suggests that the 30-day mortality among the patients with *S. maltophilia* bacteraemia who did not receive empirical antibiotics before the antibiotic sensitivity was performed to identify susceptibility to specific antibiotics had statistically significant mortality in comparison to those who received appropriate empirical antibiotics. However, studies conducted by Garcia Paez JI et al., and Insuwan W et al., suggested that the administration of inappropriate empirical antibiotics had a significance on the mortality of the patient [9,23]. The contrast in the evaluation was observed due to varying patterns of antibiotic resistance in different geographical settings. The sensitivity of both Cotrimoxazole and Levofloxacin was reported as 84.62% in this study, while in other studies, their sensitivity showed a variance of 21% to 85% [3,29].

This study not only demonstrates the clinical outcome of the patients suffering from *S. maltophilia* bacteraemia but also demonstrates the non-clinical outcomes of these patients by taking into account the length of hospital stay and time of positivity of blood culture bottles from admission, which indicates the nosocomial nature of the infection. This study identifies patients undergoing chemotherapy as a significant risk factor, and increased levels of procalcitonin served as a definite sign of sepsis among the patients who succumbed to *S. maltophilia* bacteraemia. We demonstrated the effect of the rampant empirical use of Carbapenems among the patients admitted to various medicine, surgical, and intensive care wards, which has facilitated infections with intrinsically resistant microorganisms like *S. maltophilia*. According to this observation, the most appropriate first-line drugs sensitive to the isolate in question are Levofloxacin and Cotrimoxazole. In case of resistance to the above-mentioned antibiotics, Minocycline and Ticarcillin-clavulanic acid were effective against most isolates. Appropriate use of antibiotics and antibiotic stewardship measures can be used to curb the emergence of drug-resistant isolates like *S. maltophilia*. Following strict infection control measures, maintaining stringent hand hygiene among the healthcare staff and doctors promotes a decline in the spread of multidrug-resistant infections caused by *S. maltophilia* among the immunocompromised patients admitted to various wards of the university hospital.

Limitation(s)

This study had several limitations. Firstly, the study was conducted at a single center; therefore, these findings may not be generalisable to the entire population of a geographic area. Secondly, the study focused solely on bacteraemia and pulmonary infections, neglecting other types of infections. Thirdly, there was a lack of information about the clinicians' practices regarding the initiation of empirical antibiotic therapy. Lastly, this study followed a retrospective design, which carries an increased risk of selection and information bias. Due to the time-bound nature of the present study, a statistically calculated sample size was not used.

CONCLUSION(S)

The present study identifies patients undergoing chemotherapy as a significant risk factor, and increased levels of procalcitonin serve as a definitive sign of sepsis among patients who succumbed to *S. maltophilia* bacteraemia. The widespread empirical use of Carbapenems among patients admitted to the wards has facilitated infections with intrinsically resistant microorganisms like *S. maltophilia*. The use of appropriate empirical antibiotics can reduce the length of hospital stay, as well as the 14-day and 30-day mortality rates among patients.

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