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

**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 maltophilia* 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.

**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 fluorquinolones 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 that predispose patients to adverse outcomes.
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 bacteraemia 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 Epsilometeric-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 ticloplatin 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.

<table>
<thead>
<tr>
<th>Departments where incidence of Stenotrophomonas bacteraemia was noted</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOAesthesia</td>
<td>2 (5.13%)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>COM</td>
<td>2 (5.13%)</td>
</tr>
<tr>
<td>CVTS</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Emergency</td>
<td>3 (7.69%)</td>
</tr>
<tr>
<td>Endocrine surgery</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>5 (12.82%)</td>
</tr>
<tr>
<td>Haematology</td>
<td>5 (12.82%)</td>
</tr>
<tr>
<td>Hepatology</td>
<td>3 (7.69%)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>6 (15.38%)</td>
</tr>
<tr>
<td>Neurology</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Paediatric gastroenterology</td>
<td>3 (7.69%)</td>
</tr>
<tr>
<td>Pulmonary medicine</td>
<td>2 (5.13%)</td>
</tr>
<tr>
<td>Surgical gastroenterology</td>
<td>4 (10.26%)</td>
</tr>
</tbody>
</table>

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%.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years); mean±SD (range)</td>
<td>46.0±20.29 (1-74)</td>
</tr>
<tr>
<td>Male gender</td>
<td>27 (69.23%)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Central venous catheters</td>
<td>21 (53.8%)</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>3 (7.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Haematologic malignancy</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>Pulmonary infections</td>
<td>18 (46.2%)</td>
</tr>
<tr>
<td>Mechanical ventilation/intubation</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>Nervous system diseases</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>11 (28.2%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6 (15.4%)</td>
</tr>
</tbody>
</table>
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: 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.

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.

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.
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.

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 Alonso A and Martinez JL [21, 22].

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, Cefazidime 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 Insuwanw W et al., suggested that the administration of inappropriate empirical antibiotics had a significant impact 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 medical, 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 generalizable 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.

Procalcitonin (normal range <0.5 μg/L)

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.94±5.90</td>
<td>0.66±0.80</td>
<td>12.28±4.90</td>
</tr>
</tbody>
</table>

Leukocytes (normal range 4,000-10,000/μL)

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15729.28±6346.74</td>
<td>15061.36±6243.11</td>
<td>17378.55±6607.90</td>
</tr>
</tbody>
</table>

[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.

[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).
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 bacteremia. 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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REFERENCES