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*Original Article*

# Rising threats of hospital-borne multidrug resistant *Stenotrophomonas maltophilia* in the adolescent at Najran, Saudi Arabia

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## Abstract

Introduction: The aim of this study was to investigate the clinical isolates of patients infected by *Stenotrophomonas maltophilia* (*S. maltophilia*) in the intensive care unit (ICU) at King Khalid Hospital, Kingdom of Saudi Arabia (KSA), and to identify the healthcare complications, antimicrobial resistance patterns, and risk factors associated with infection for this emerging pathogen.

Methodology: In this cross-sectional observational study, patients admitted in the ICU (n = 127) were analyzed, and 36 non-duplicating *S. maltophilia* strains were clinically isolated in King Khalid Hospital, KSA between September 2020 and April 2021. Antimicrobial susceptibility testing was performed using standard antibiotics (n = 13).

Results: In this study, 36 clinical isolates of *S. maltophilia* were identified as true infection pathogens. The main locations of *S. maltophilia* infection were in the respiratory tract (13, 36.1%) followed by surgical area (10, 27.7%) and wound infection (7, 19.4%). The significant risk factors included a medical history of respiratory infection, exposure to a bomb blast, and infected from an implant ($p < 0.05$). Among the 36 clinical isolates, 5 strains were positive for extended spectrum beta-lactamase (ESBL). The most active antimicrobials were vancomycin (69.4% sensitivity) and trimethoprim/sulfamethoxazole (80.5% sensitivity).

Conclusions: Our study concludes that *S. maltophilia* is an emerging nosocomial pathogen in the ICU, indicating the possibility of direct or indirect transfer from one person to another. Specific identification and active antibiotic susceptibility testing of *S. maltophilia* are needed for the treatment management and prevention of spread of the *S. maltophilia* pathogen.

**Key words:** adolescent; healthcare-acquired; multidrug resistance; nosocomial infection; *Stenotrophomonas maltophilia*.

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## Introduction

*Stenotrophomonas maltophilia* (*S. maltophilia)* is a developing commensal pathogen previously identified in broad-spectrum life-threatening infections but has recently been identified as a serious pathogen in immunocompetent people [1]. Necrotizing otitis, cutaneous infections such as soft tissue infection and keratitis, endocarditis, meningitis, acute respiratory tract infection (RTI), bacteremia (with/without hematological malignancies), tropical pyomyositis, cystic fibrosis, and septic arthritis are a few conditions that are frequently linked to *S. maltophilia* [2]. It is a common environmental bacterium that can be found in food, water, rhizospheres, animal microflora, and other microbiota.

*S. maltophilia* has recently become a significant nosocomial opportunistic infection among juvenile patients. After *Pseudomonas aeruginosa* and *Acinetobacter species*, *S. maltophilia* is now the third most frequent non-fermentative Gram-negative bacilli causing nosocomial infections globally [3]. In hospitalized patients, particularly in intensive care units (ICUs), *S. maltophilia* has become a significant cause of morbidity and mortality. This organism was formerly assigned to the genus *Pseudomonas maltophilia*. In 1993, it was moved to the genus *Xanthomonas*, and later became the only member of the genus *Stenotrophomonas* [4]. The pathogen is likely tied to improvements in medical care that have increased the number and survival rates of children who are very ill and disabled, and who are the vulnerable population most at risk for contracting this pathogen. There are numerous clinical manifestations of *S. maltophilia*. The most frequent infections described in numerous clinical and epidemiological investigations are respiratory tract infections, particularly ventilator-associated pneumonia (VAP) and bloodstream infection (BSI). To ensure consistency in the data collected, the Centers for Disease Control and Prevention (CDC) / National Healthcare Safety Network (NHSN) criteria were

utilized to determine whether or not an isolate was contagious. Furthermore, when *S. maltophilia* is not the sole organism recovered, determining the presence of a true *S. maltophilia* infection could be more difficult [3]. Examining episodes of infection from non-respiratory locations, it was found that 70.6% of *S. maltophilia* isolates were from poly-microbial cultures that also produced other obligate pathogens (*Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella species,* and *Acinetobacter species*) [5]. The large percentage of poly-microbial isolation in most investigations, the co-isolation of pathogens that are well known to cause infection at these sites, and the high cure rate despite inadequate therapy all cast doubt on the importance of *S. maltophilia* in the etiology of poly-microbial infections.

The *S. maltophilia* control arsenals face significant obstacles from low outer membrane permeability, natural multidrug resistant (MDR) efflux systems and/or resistance genes, resistance mechanisms such as the creation of two inducible chromosomally encoded lactamases, and a lack of thoroughly recorded patient histories [6]. Fluoroquinolone, a few tetracycline derivatives, and trimethoprim-sulphamethoxazole (TMP-SMX) have all been identified as effective antibiotics with positive therapeutic outcomes. However, significant drawbacks include TMP-SMX resistance, sulfa allergies, and high fluoroquinolone toxicity. Quorum quenching is a crucial step in *Stenotrophomonas* control because *S. maltophilia's* development and maintenance of biofilm by quorum sensing increase their virulence, tolerance to antibiotics, and gene transfer. The use of cationic chemicals, bioengineered bacteriophage therapy, epigallocatechin-3-gallate (EGCG), essential oils, nanoemulsions, and other tried-and-true techniques can be added to the arsenal of strategies for controlling *Stenotrophomonas* species [7]. Given the importance of identifying and managing the infections of *S. maltophilia*, we investigated our hospital in-patients in a clinical study on antibiotic sensitivity and the rate of infectivity.

## Methodology

*Study setting*

The medical records of the patients in the ICU at King Khalid Hospital - Najran, a tertiary care centre in the southern region of Saudi Arabia, were reviewed for the current clinical investigation as a surveying experimental study between September 2020 to April 2021. The trial group consisted of patients with a hospital acquired infection who had spent more than 48 hours in the ICU. Data on patient outcomes, microbiology, antibiotic therapy, and demographics were collected. In this study, 532 patients with bacteraemia, pneumonia, and other infections that were classified as nosocomial infections or diseases acquired through medical care (those occurring within 48 hours of hospital admission) were included.

*Ethical approval*

The research techniques, which included collecting samples from and working with human subjects, complied with ethical standards. The Internal Review Board Committee for Ethics of King Khalid Hospital-Najran gave its ethical approval (No: 44/1/19/NU/DS. Date: 04\11\ 2019).

*Bacterial isolates*

Clinical samples from a range of illnesses in the ICU (n = 127) were prepared for culture using conventional methods. Initial identification was carried out using common phenotypic assays [8]. The VITEK 2 identification system (BioMerieux, Marcy-l'Étoile, France) was utilized in the microbiology lab to confirm the isolates following manufacturer's protocol after first identification.

The VITEK 2 system underwent antimicrobial susceptibility testing, according to the manufacturer's protocol, and was further confirmed by disc diffusion (Kirby Bauer's) technique according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [9]. The most popular drugs' *in vitro* susceptibility to the most common antibiotics (n = 14) were: ampicillin, piperacillin- tazobactam, ceftazidime-avibactam, imipenem, meropenem, ciprofloxacin, levofloxacin, amikacin, tobramycin, oxytetracycline, trimethoprim – sulfamethoxazole, rifampicin, vancomycin, colistin used for typical ICU illnesses. The zone of inhibition was measured and interpreted according to the CLSI recommendation [9].

Statistical variables were assessed by submitting the data to descriptive analysis, which comprised frequency and percent distribution, including bio-demographic data, the origin of clinical specimens, and the type of organisms to compare the trend of antimicrobial susceptibility pattern by Microsoft Excel 2019.

## Results

In our current clinical investigations, we found that the infections were persistent and gender-specific, consistently occurring in only males rather than females. *S. maltophilia* has a lot of dynamism. The organism has been described as a genuine pathogen in immunocompetent people in addition to being an

opportunistic pathogen in severe life-threatening infections. Our study initially started with 532 samples and was further narrowed down to the infections particularly caused by *S. maltophilia*. Out of 532 clinical isolates 127 were collected from the ICU (Table 1). Among the 127 clinical isolates, 36 non-duplicating *S. maltophilia* were identified and found to have the infection.

Among 127 consecutive hospitalized ICU patients during the 8-month study period, 36 (28.3%) developed a *S. maltophilia* infection and 91 (71.6%) were other isolates. All 36 *S. maltophilia* were isolated from patients who were 21 to 65 years. The mean age of the males in the *S. maltophilia* study group was 34.4 ± 4.4 years and of the females was 32.1 ± 4.2 years.

Among the *S. maltophilia* isolates, 32 (88.8%) were isolated from males and 4 (11.1%) from females. Total clinical isolates of from ICU isolated from the infection site were: wound 41 (32.2%), blood 28 (22%), respiratory tract 22 (17.3%), surgical area 17 (13.3%) and urinary tract 19 (14.9%). Isolated *S. maltophilia* from the infection site were: wound 7 (19.4%), blood 4 (11.1%), respiratory tract 13 (36.1%), surgical area 10 (27.7%) and urinary tract 2 (5.5%). The total number of clinical isolates were categorized based on the patient's medical history. Among the isolates, 7 (19.4%) were isolated from patients without any medical history, 2 (5.5%) from post-cardiac arrest patients, 13 (36.1%) from respiratory infection patents, 5 (13.8%) from diabetes mellitus patients, 6 (16.6%) from bomb blast injury patients and 4 (11.1%) from infected implants. Total isolates from the surgical site of infection were 10 (27.7%). Among the isolates, 2 (20%) were from laparotomy, 1 (10%) from incision, 3 (30%) from appendectomy and 4 (40%) from infected implant (Table 2).

**Table 2.** *Stenotrophomonas maltophilia* isolates from surgical site infections among the intensive care unit (ICU) patients.

| Site of Surgical Procedure | *Stenotrophomonas maltophilia* (n = 10) percentage |
|---|---|
| Laparotomy | 2 (20%) |
| Incision | 1 (10%) |
| Appendectomy | 3 (30%) |
| Infected Implant | 4 (40%) |
| Total | 10 (100%) |

Interestingly, our investigation showed that the highest incidence of infections occurred between the age group of 20-30 years (Figure 1A). The adolescent group is highly susceptible to infection, which is quite controversial since the pathogen is opportunistic. The incidence might be due to the non-availability of age-matched patients in our clinical study. Figure 1B depicts them as primary infection with co-morbidity and ESBL positive *S. maltophilia* isolates 5 (13.8%).

Our clinical investigation data suggested that the isolated *S. maltophilia* had a wide range of antibiogram sensitivity patterns (Table 3). The isolated strains were resistant to ampicillin, imipenem, meropenem, amikacin, levofloxacin, tobramycin, oxytetracycline, and rifampicin whereas, it showed an intermittent pattern with vancomycin. Among clinical specimens, the highest resistance was to ampicillin (77.7%), imipenem (72.2%), meropenem (69.4%), and levofloxacin (69.4%) and the lowest resistance was to

**Table 1.** Demographics and Clinical data of the total study group, *Stenptrophomonas* species isolated from intensive care unit (ICU).

| Variable | Total group (n = 127) | *Stenotrophomonas maltophilia* (n = 36) |
|---|---|---|
| Total number of isolated microorganisms from ICU | 127 (100) | 36 (100%) |
| **Age (years)** | | |
| Male | 45.4 ± 4.3 | 34.8 ± 4.4* |
| Female | 41.8 ± 4.4 | 32.1 ± 4.2 |
| **Gender** | | |
| Male | 89 (70.1%) | 32 (88.8%)* |
| Female | 38 (29.9%) | 4 (11.1%)* |
| **Site of the Infection** | | |
| Wound | 41 (32.2%) | 7 (19.4%)* |
| Blood | 28 (22%) | 4 (11.1%)* |
| Respiratory tract | 22 (17.3%) | 13 (36.1%)* |
| Surgical area | 17 (13.3%) | 10 (27.7%)* |
| Urinary tract | 19 (14.9%) | 2 (5.5%)* |
| **Diagnosis history** | | |
| No medical history | 49 (38.5%) | 7 (19.4%)* |
| Post Cardiac Arrest | 7 (5.5%) | 2 (5.5%) |
| Respiratory | 23 (18.1%) | 13 (36.1%)* |
| Diabetes mellitus | 38 (29.9%) | 5 (13.8%)* |
| Bomb blast injury | 6 (4.7%) | 6 (16.6%) |
| Infected Implant | 4 (3.1%) | 4 (11.1%) |

* Represents the statistically significant. All comparisons were 2-tailed, and $p$ values < 0.05 were considered statistically significant.

trimethoprim–sulfamethoxazole (8.3%), whereas all the clinical isolates were susceptible to trimethoprim–sulfamethoxazole 29 (80.5%) and vancomycin 25 (69.4%) (Table 3). Twenty-three of the 36 isolates (63.8%) were multi drug resistant (MDR) (resistant to ≥ 3 classes of antibiotics).

Among clinical isolates, the highest resistance was to ampicillin (77.7%), imipenem (72.2%), meropenem (69.4%), and levofloxacin (69.4%) and the lowest resistance was to trimethoprim–sulfamethoxazole (8.3%), whereas isolated clinical isolates 25 (69.4%) were susceptible to and 9 (25%) were intermediate to vancomycin (Table 3). Eighteen of the 36 isolates (63.8%) were MDR (resistant to ≥ 3 classes of antibiotics).

## Discussion

*S. maltophilia* has a lot of dynamism. The organism has been described as a genuine pathogen in immunocompetent people in addition to being an opportunistic pathogen in severe life-threatening infections in the weak. Particularly when it comes to clinical disorders like cystic fibrosis, bacteraemia, and/or urinary tract infections, among others, this bacterial species is linked to illnesses and mortality from RTI. As arbitrary antibiotic therapy may enhance myelosuppression and/or select resistant strains of the species, an accurate diagnosis with sufficient caution is essential. Low outer membrane permeability, innate MDR efflux systems, and resistance mechanisms like the synthesis of two inducible chromosomally encoded lactamases all contribute to *S. maltophilia*'s inherent resistance to antimicrobials [1].

**Figure 1 A:** Age-wise representation of infection incidence; **B:** Representation of infection history with other morbidity conditions.

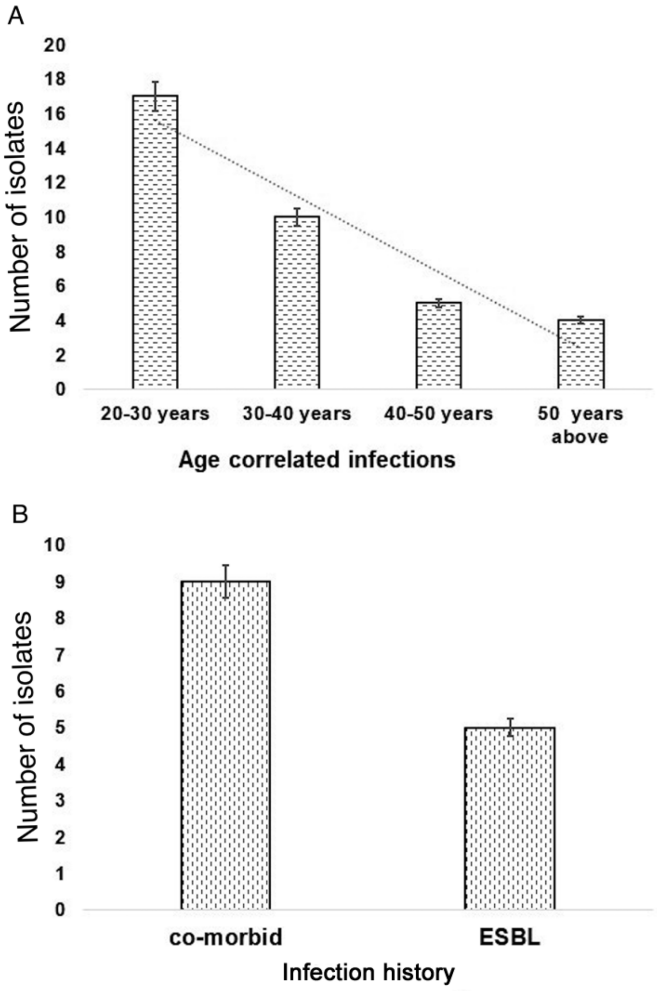


**Table 3.** Antibiogram test pattern of *Stenotrophomonas maltophilia* isolated from clinical samples.

| Group | Members | *S. maltophilia* isolated from clinical samples (n = 36) | | | | | |
|---|---|---|---|---|---|---|---|
| | | S | | I | | R | |
| | | No | % | No | % | No | % |
| **Penicillin derivatives** | Ampicillin | 5 | 13.8% | 3 | 8.3% | 28 | 77.7% |
| | Piperacillin- Tazobactam | 12 | 33.3% | 8 | 22.2% | 16 | 44.4% |
| **Cephalosporines** | Ceftazidime- Avibactam | 20 | 55.5% | 0 | 0% | 16 | 44.4% |
| **Carbapenems** | Imipenem | 6 | 16.6% | 4 | 11.1% | 26 | 72.2% |
| | Meropenem | 6 | 16.6% | 5 | 13.8% | 25 | 69.4% |
| **Quinolones** | Ciprofloxacin | 8 | 22.2% | 9 | 25% | 19 | 52.7% |
| | Levofloxacin | 10 | 27.7% | 1 | 2.7% | 25 | 69.4% |
| **Aminoglycosides** | Amikacin | 14 | 38.8% | 4 | 11.1% | 18 | 50% |
| | Tobramycin | 9 | 25% | 5 | 13.8% | 22 | 61.1% |
| **Tetracyclines** | Oxytetracycline | 8 | 22.2% | 5 | 13.8% | 23 | 63.8% |
| **Sulfonamides** | Trimethoprim –Sulfamethoxazole | 29 | 80.5% | 4 | 11.1% | 3 | 8.3% |
| **Rifamycins** | Rifampicin | 14 | 38.8% | 0 | 0% | 22 | 61.1% |
| **Glycopeptides** | Vancomycin | 25 | 69.4% | 9 | 25% | 0 | 0% |
| **Polypeptides** | Colistin | 16 | 44.4% | 8 | 22.2% | 12 | 33.3% |

In our view, the organism should be reclassified as a pathogen and used as one of the test isolates in the development of antibacterial drugs in order to prevent the imminent hazard in the arsenal of *S. maltophilia* control measures. As these circumstances predispose the organism to antibiotic resistance, strict attention to hygienic norms, quality control in medical units and pharmaceutical businesses, preventing the abuse of antibiotics, etc is needed. The bacterium may have antimicrobial resistance genes that can spread to other species, endangering public's health.

Presence of cardiovascular complications (CVC), neutropenia, ICU stay, mechanical ventilation or tracheotomy, prior history of antibiotic therapy, underlying illness, and prolonged hospitalization were among risk factors that are predisposed to acquire *S. maltophilia* infections [10]. The fact that acute leukemia was identified as the primary underlying condition linked to *S. maltophilia* infection is very significant. However, researchers discovered that among pediatric patients in their analysis, preterm, primary immunodeficiency, and congenital heart disease were distinct and more frequent risk factors. Contrary to numerous earlier research, exposure to antibiotics was known to be caused by both colonized and infected. One of the antibiotic groups most frequently linked to the isolation of *S. maltophilia* is the carbapenem family. Other groups of antibiotics, such as ampicillin, gentamicin, vancomycin, metronidazole, piperacillin, cephalosporins, and tobramycin, have been linked in multiple studies as important risk factors for the colonization and infection of *S. maltophilia* [11]. In our hospital, nosocomial infections in children and adults are treated based only on the empirical use of cephalosporins, carbapenems, and aminoglycosides. As many clinical strains of *S. maltophilia* exhibit both intrinsic resistance to different classes of antibiotics like carbapenems and aminoglycosides and induced resistance to fluoroquinolones, which are used indiscriminately for nosocomial sepsis, the management of *S. maltophilia*-associated infection is challenging. Trimethoprim/sulfamethoxazole seems to be the antibiotic most effective against infections brought on by *S. maltophilia* [12].

Due to their resistance to most antimicrobial drugs and the varied antimicrobial susceptibility of various strains, treating infections caused by these organisms is difficult. However, it is advised to combine ticarcillin-clavulanic acid and trimethoprim-sulfamethoxazole for early empirical use. Even the expanded-spectrum cephalosporin cefpirome, more recent quinolones like levofloxacin and gatifloxacin, and the most recent formulations of -lactam-lactamase inhibitors failed to effectively treat the infection [13]. Meropenem, a carbapenem that has only lately been made available in our nation and is not yet frequently used in hospitals, was utilized to successfully treat meropenem, carbapenem infections.

Recent studies indicate that infections related to humans or healthcare will continue to adapt and spread globally. In order to determine population structure and clonality on a worldwide scale, a study examined a sample of the developing, MDR, opportunistic pathogen *S. maltophilia* from 22 different countries. It demonstrated the existence of 23 monophyletic lineages within the *S. maltophilia* complex, the majority of which contain strains with varying levels of human pathogenicity. The majority of strains associated with humans are found in lineage Sm6, which is connected with important virulence and resistance genes. Through the use of transmission analysis, it is possible to spot outbreaks caused by genetically similar germs that were isolated in the same hospitals within a short period of time [14-16].

Among the other developing infections, *S. maltophilia*, which the World Health Organization (WHO) lists as one of the most common drug-resistant nosocomial pathogens worldwide, lacks global genome-based collections [17]. *S. maltophilia* is commonly found in natural habitats and is significant for the industry and environmental cleanup. With an attributable mortality rate of up to 37.5% in immunocompromised patients, *S. maltophilia* is a substantial contributor to hospital-acquired drug-resistant infections. Those who are using an immunosuppressive medication, have cancer, or already have inflammatory lung illnesses such as cystic fibrosis are particularly at risk for contracting *S. maltophilia.*

This study provides valuable insight into the predisposing factors associated with *S. maltophilia* infection. The results of this study are similar to those reported by other studies that mainly focused on *S. maltophilia* isolations among adult patients [18-20]. These risk factors included prolonged hospitalization, patients who had undergone implant, ICU admission, prior antibiotic therapy, tracheotomy, and respiratory infection. These findings suggests that *S. maltophilia* infection is more common among elderly people, men, and those with underlying medical conditions. Fihman *et al.* [21] reported that other classes of antibiotics including gentamicin, ampicillin, metronidazole, vancomycin, cephalosporins, piperacillin, and tobramycin, as one of the significant threats to

colonization and infection of *S. maltophilia*. In the previous decades, research has shown that the overall prevalence of SXT resistance among the clinical isolates of *S. maltophilia* strains is increasing which is comparable with our reports [22-24].

Our study shows the antimicrobial resistance pattern to SXT among *S. maltophilia* strain was 8.3%, while it was 3.7% in the USA and 2.3% in Europe and the Mediterranean region (EMR) [25] whereas, the rates of trimethoprim/sulfamethoxazole resistance have been reported in the Asia-Pacific region to be between 8-18% to which our data were comparable [26]. In a recent study in Saudi Arabia, two clinical isolates of *S. maltophilia* were trimethoprim/sulfamethoxazole-resistant, whereas in our study resistant clinical isolates of *S. maltophilia* strains were increased into three [24,27]. In this study, vancomycin was the most active antimicrobial drug against *S. maltophilia* isolates (69.4% susceptibility), second to trimethoprim/sulfamethoxazole. These findings highlight the in vitro activity of vancomycin against *S. maltophilia* and this antibiotic can be used as alternative empiric therapy for *S. maltophilia* infection.

Despite the fact that practically any organ may be impacted, mere colonization must be distinguished from infections that typically present as bacterial infections, respiratory tract infections, or bloodstream infections associated with catheters. However, the bacterium is also frequently isolated from wounds and, less frequently, from infections linked to implants. Infections that are acquired in the community have also been documented. Treatment choices are constrained by resistance to many antimicrobial classes, including the intrinsic resistome, genetic material obtained through horizontal transfer, and non-heritable adaptive mechanisms, which include most -lactam antibiotics, cephalosporins, aminoglycosides, and macrolides.

The population structure and clonality of *S. maltophilia* in connection to human disease have not yet been the subject of extensive genome-based studies on a broad scale. The bloodstream infection-related strain of *S. maltophilia* known as K279a serves as an indicator strain for the *S. maltophilia* sensu stricto lineage. *S. maltophilia* infection prevention and control in clinical settings would be significantly impacted by the discovery of widely dispersed clonal complexes or probable epidemic occurrences of *S. maltophilia* complex strains. The existence of transmission clusters in strains associated with humans, indicating the possibility of direct or indirect transfer from one person to another. In those instances where comprehensive epidemiological data regarding the hospital and the day of isolation was available, a common source of infection was supported. The handling of *S. maltophilia* colonization or infection by infection prevention and control teams would be significantly impacted by further research into potential transmission events.

Our study conducted at a single center has certain potential limitations due to the limited number of *S. maltophilia* isolates. Consequently, to gain a better understanding of the prevalence and distribution of *S. maltophilia* associated infections and curb the spread of multi-drug resistant nosocomial isolates, it is imperative to conduct further epidemiological studies at multiple centers for a longer surveillance duration.

## Conclusions

One of the less well-known drug-resistant bacteria that can produce difficult illnesses is *S. maltophilia*. The study demonstrates that *S. maltophilia* causes a considerable percentage of nosocomial infection, especially in respiratory tract infections in ICUs. The percentage of multidrug resistant isolates was high. Trimethoprim-sulfamethoxazole and vancomycin are the recommended drugs of choice for the treatment of *S. maltophilia* infections. The isolation of trimethoprim-sulfamethoxazole and vancomycin-resistant isolates in our hospitals was alarming. *S. maltophilia* infection prevention and control in clinical settings would be significantly impacted by the discovery of widely dispersed clonal complexes or probable epidemic occurrences of *S. maltophilia* complex strains. The existence of transmission clusters in strains associated with humans indicates the possibility of direct or indirect transfer from one person to another. In those instances where comprehensive epidemiological data regarding the hospital and the day of isolation was available, a common source of infection was supported. The handling of *S. maltophilia* colonization or infection by infection prevention and control teams would be significantly impacted by further research into potential transmission events.

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