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Review article

Stenotrophomonas maltophilia: Serious Clinical Pathogen

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ABSTRACT

In recent years, the bacterial pathogen *Stenotrophomonas maltophilia* has emerged as a significant clinical concern, challenging healthcare providers and researchers alike. Once considered an opportunistic pathogen of limited clinical importance, this gram-negative bacterium is increasingly recognized as a formidable adversary, particularly in individuals with compromised immune systems, chronic respiratory conditions, or those undergoing invasive medical procedures. A fundamental aspect of its clinical success lies in its ability to adhere to biotic and abiotic surfaces within the host environment, facilitating colonization and subsequent infection. In this review, we delve into the intricate world of *S. maltophilia*, exploring its taxonomy, morphology, genetic characteristics, ecological habitat, clinical manifestations, respiratory tract infection, bacterial pneumonia, *S. maltophilia* and Cystic fibrosis, malignant tumor, and *S. maltophilia* and Hospital-Acquired Infections (HAI).

Keywords: Immunocompromised patients, Opportunistic pathogen, Respiratory tract, *Stenotrophomonas maltophilia.*

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1. INTRODUCTION

Stenotrophomonas maltophilia is an opportunistic pathogen, the pathogenicity of this bacteria has gained increasing attention in recent years due to its pathogenic potential, particularly in individuals with compromised immune systems. This bacterium causes a range of infections in humans [1]. It is a Gram-negative, rod-shaped bacterium. It is naturally found in various environmental sources, such as water, soil, and plants. In these settings, it plays a role in biodegradation and can be beneficial. However, when it enters the human body, especially in individuals with weakened immune defenses, it can become a formidable pathogen. It is considered an opportunistic pathogen, meaning it primarily infects patients who are already immunocompromised or have underlying medical conditions [2]. This includes patients with cystic fibrosis, cancer, chronic respiratory diseases, or those who have undergone organ transplantation. It can also infect patients in healthcare settings, particularly those on ventilators or with indwelling catheters [3]. It is capable of causing a variety of infections, including pneumonia, bloodstream infections, urinary tract infections, and wound infections. Symptoms can range from mild to severe, with fever, cough, and difficulty breathing being common in respiratory infections [4]. In bloodstream infections, it can lead to sepsis, a life-threatening condition. One of the significant challenges in dealing with *S. maltophilia* infections is its intrinsic resistance to many antibiotics. This bacterium often exhibits resistance to multiple classes of antibiotics, making treatment difficult and limited in options. This resistance is due in part to its ability to form biofilms, protective communities of bacteria that shield it from antibiotics and the immune system. *S. maltophilia* infections require a multidisciplinary approach. Combination antibiotic therapy, sometimes involving newer agents may be effective. However, treatment decisions should be based on antimicrobial susceptibility testing [5]. The pathogenicity of *S. maltophilia* is ongoing, with a focus on understanding its virulence

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factors, antibiotic resistance mechanisms, and potential therapeutic strategies. As the prevalence of multidrug-resistant pathogens continues to rise, *S. maltophilia* remains a concerning bacterium in the realm of healthcare-associated infections. It poses a significant challenge to healthcare providers due to its capacity to cause a range of infections, especially in immune-compromised individuals [6].

2. TAXONOMY

S. maltophilia (*Stenos*, Greek: narrow; *trophos*, Greek: one who feeds; *monas*, Greek: a unit, monad; i.e., a unit feeding on few substrates; and *malt*, old English: malt; *philos*, Greek: friend; i.e., a friend of malt). The type strain was isolated in 1958 by Hugh from an oropharyngeal swab of a patient with oral carcinoma and named *Pseudomonas maltophilia*. Subsequently further proposed that *P. maltophilia* be reclassified in the genus *Xanthomonas* as *X. maltophilia*. Continuing dissatisfaction with the classification of this organism finally gave rise to a proposal in 1993 to create a new genus *Stenotrophomonas* with *S. maltophilia* as its sole member [7,8].

3. MORPHOLOGY

S. maltophilia are slightly smaller (0.7-1.8 x 0.4-0.7 µm), straight or slightly curved, non-sporulating gram-negative bacilli. They are motile due to polar flagella and grow well on agar-producing pigmented colonies. *S. maltophilia* are catalase positive, and oxidase negative (which distinguishes them from most other members of the closely related genera) and show positive reactions for extracellular DNase [9].

4. GENETIC CHARACTERISTICS

The genome of *S. maltophilia* K279a is 4,851,126 bp and possesses high G+C content. The sequence reveals an organism with a remarkable capacity for drug and heavy metal resistance, in addition to a number of genes conferring resistance to antimicrobial drugs of different classes via alternative mechanisms. Functional genome analysis confirms a role in drug resistance for several antibiotics such as gentamycin, ciprofloxacin, levofloxacin, ceftazidime, cefepime; ticarcillin/clavulanic acid, piperacillin/tazobactam, aztreonam; and meropenem [10]. *S. maltophilia* possesses potentially mobile regions of DNA and encodes a number of pili and fimbriae, likely to be involved in adhesion and biofilm formation that indirectly may also contribute to increased antimicrobial drug resistance [11].

5. HABITAT

S. maltophilia is found in a wide variety of environments and geographical regions, including Antarctica [12], and occupies ecological niches both inside and outside hospitals. It has been isolated from a number of water sources including rivers, wells, hypereutrophic lakes, bottled water, and sewage [13]. The bacterium has also been recovered from a variety of soils and plant rhizosphere environments, including grasses, sugarcane, and palms [2, 14].

6. EPIDEMIOLOGY

S. maltophilia was considered an unusual organism to be isolated in the diagnostic microbiology laboratory, despite earlier claims that it was the second most common non-fermentative Gram-negative bacillus (after *P. aeruginosa*) isolated from clinical specimens [7]. Isolation rates have been increasing since the early 1970s. Detailed comparisons between studies which have analyzed predisposing factors are not possible for a number of reasons. These include variations in patient mix, criteria used to define infection, and statistical methods used to analyze data. It is noteworthy, however, that in many of these studies, prior exposure to antimicrobial agents has been consistently associated with *S. maltophilia* infection and that nearly all of them are indicative of patient debilitation [15]. Several nosocomial outbreaks of *S. maltophilia* infection and/or colonization have now been described. In several instances, putative environmental reservoirs for the bacterium have been identified [16]. Contaminated deionized water used to make disinfectant was found to be responsible for the *S. maltophilia* outbreak which involved 63 patients in an Australian hospital; four cases of septicemia with *S. maltophilia* were attributed to inadequate disinfection of reusable capillary dialyzers [17].

7. CLINICAL MANIFESTATIONS of *S. maltophilia* INFECTIONS

S. maltophilia is associated with an ever-expanding spectrum of clinical syndromes [7]. However, many early publications failed to cite unequivocal evidence for infection with this organism. *S. maltophilia* has emerged as an important opportunistic pathogen in debilitated hosts. *S maltophilia* is not an inherently virulent pathogen, but its ability to colonize respiratory tract epithelial cells [2,4] and surfaces of medical devices makes it a ready colonizer for hospitalized patients. *S. maltophilia* can cause bloodstream infections and pneumonia with considerable morbidity in immunosuppressed patients [18]. Management of infection is hampered by high-level intrinsic resistance to many antibiotic classes and the increasing occurrence of acquired resistance to the first-line drug co-trimoxazole. Prevention of acquisition and infection depends upon the application of modern infection-control practices, with emphasis on the control of antibiotic usage and environmental reservoirs [19]. An increasing incidence of *S. maltophilia* isolates has been reported in some CF centers during the last decade [20]. Although an association between *S. maltophilia* colonization and lung damage has been observed, the role of this organism is still undetermined in lung damage [7]. In non-CF patients, exposure to wide-spectrum antimicrobial drugs, long-term antimicrobial therapy, previous pulmonary infections, and chronic respiratory disease contribute to *S. maltophilia* acquisition and increase the risk for respiratory infection with this organism. *S. maltophilia* is a common colonizer of the respiratory tract of patients with chronic lung disease, and, in the absence of pneumonia or bacteremia, is often ignored by physicians as there was no measurable impact of antibiotic therapy, in the absence of consolidation, a respiratory tract isolate of *S. maltophilia* probably represents colonization of a severely impaired host rather than an invasive disease [17]. A distinction between *S. maltophilia* colonization and infection is made even more difficult by the frequent isolation of other organisms from the same specimen. Therefore, although there is good evidence that *S. maltophilia* causes significant mortality in patients with nosocomial pneumonia [21] in other clinical settings, the significance of respiratory isolate is much less clear.

Several case-control studies have drawn conflicting conclusions regarding the role of *S. maltophilia* in the pathogenesis of the infection process. In human medicine, *S. maltophilia* is recognized as a nosocomial pathogen, isolated primarily from immunocompromised patients [6]. Although occasionally considered a contaminant, or possibly a commensal, in clinical material, it is generally accepted that this bacterium can behave as a true pathogen [22].

The colonization of bacteria is the first step to cause infection. There is much similarity between *S. maltophilia* and related bacteria like *P. aeruginosa* and *B. cepacia,* the latter are known to possess more virulence properties as compared to *S. maltophilia.* This is possibly the reason that *S. maltophilia* infections are reported only in patients suffering from immunosuppression-associated diseases like CF [20]. The studies in our laboratory on different clinical isolates of *S. maltophilia* showed the ability of these bacteria to adhere to viable epithelial cells obtained from LACA mice. Chhibber *et al.* (2008) found that *S. maltophilia* can produce some virulence factors like protease and lipase but the clinical isolates of *S. maltophilia* have been shown to be noninvasive [23]. Despite the lack of invasiveness, *S. maltophilia* has immune-stimulatory properties as induction of TNF-α expression specifically indicates that it is likely to contribute significantly to airway inflammation [24]. However, the clinical conditions in which this organism has an important role to play include bacteremia, and endocarditis [25], respiratory tract [17,20] and ophthalmic infections [7]. Infections of the urinary tract, skin, soft tissue, bone, joint, gastrointestinal tract, and central nervous system are also common [7].

7.1. Respiratory tract infection

S. maltophilia has been reported to account for 5 % of nosocomial pneumonia. Nosocomial pneumonia has been observed during outbreaks of *S. maltophilia* infection, with several cases occurring over relatively short periods [7]. The respiratory tract is the most common site of isolation of *S. maltophilia* in hospitalized patients, accounting for the origin of 56 to 69 % of isolates, although the majority of patients (53 to 71%) with *S. maltophilia*-positive respiratory tract cultures are colonized rather than infected at this site [7]. More rigorous diagnostic criteria are therefore necessary, if a distinction between colonization and true infection is to be made [26]. *S. maltophilia* nosocomial pneumonia is associated with mechanical ventilation, tracheostomy, previous exposure to broad-spectrum antibiotics, use of respiratory tract equipment such as nebulizers [27], and therapy with aerosolized polymyxin. Respiratory tract involvement with *S. maltophilia* is associated with significantly increased mortality. It was reported that isolation of a “high-risk” pathogen such as *S. maltophilia* was the most important predictor of mortality in late-onset ventilator-associated pneumonia. The mortality rate in neutropenic patients with pneumonia is 40% [7]. In one *in vitro* study of *S. maltophilia* and influenza, it was concluded that co-infection with *S. maltophilia* could enhance the pathogenicity of the equine influenza virus [28].

7.2. Bacterial pneumonia

Bacteria typically enter the lung when airborne droplets are inhaled, but can also reach the lung through the bloodstream when there is an infection in another part of the body. Many bacteria live in parts of the upper respiratory tract, such as the nose, mouth, and sinuses, and can easily be inhaled into the alveoli. Once inside, bacteria may invade the spaces between cells and between alveoli through connecting pores. This invasion triggers the immune system to send neutrophils to the lungs. The neutrophils engulf and kill the offending organisms, and also release cytokines, causing a general activation of the immune system [29]. This leads to fever, chills, and fatigue, the symptoms common in bacterial and fungal pneumonia. The neutrophils, bacteria, and fluid from surrounding blood vessels fill the alveoli and interrupt normal oxygen transportation.

The types of Gram-negative bacteria that cause pneumonia can be found in the nose or mouth of many healthy people. *Streptococcus pneumoniae*, often called "pneumococcus", is the most common bacterial cause of pneumonia in all age groups except newborn infants. Pneumococcus kills approximately one million children annually, mostly in developing countries [30]. Another important gram-positive cause of pneumonia is *Staphylococcus aureus.* Some of the Gram-negative bacteria that cause pneumonia include *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa,* and *Moraxella catarrhalis*. *S. maltophilia* is responsible for pneumonia infection in debilitated persons [31]. "Atypical" bacteria that cause pneumonia include *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* [32].

Several studies focused on the cases of pneumonia caused by a mucoid *S. maltophilia* (*X. maltophilia*) strain in a patient with bronchiectasis. The patient was admitted because of mild hemoptysis and productive cough with infiltrative shadow in the right lower lung field on chest X-ray. The clinical symptoms were mild and treatment with minocycline was effective. Gasparetto *et al.* (2007) found the culture of the material obtained from bronchoalveolar lavage, collected from patients who underwent bone marrow transplantation, positive for *S. maltophilia*. The patients rapidly presented respiratory insufficiency and death on the same day [33].

Patients undergoing hemodialysis are immunocompromised and can suffer from pneumonia with various pathogens in hospital settings. They suffer from nosocomial pneumonia caused by multi-drug resistant pathogens, including *S. maltophilia* [6]. *S. maltophilia*, related pneumonia should be treated very carefully because of its high fatality rate. *S. maltophilia* pneumonia is also commonly associated with concomitant polymicrobial colonization or infection. Underlying co morbidities and inadequate initial empirical antibiotic therapy substantially account for increased mortality rates [34]. Increasing incidence of *S. maltophilia* isolates from patients suffering from pneumonia during the previous years is due to the ability of *S. maltophilia* to adhere to biotic and abiotic surfaces [35]. Previous studies showed the ability of *S. maltophilia* to cause pneumonia in experimental animals [36].

7.3. S. maltophilia and Cystic fibrosis

S. maltophilia is a gram-negative bacterium that can be associated with respiratory infections in individuals with cystic fibrosis (CF). Cystic fibrosis is a genetic disorder that affects the lungs and other organs, leading to the production of thick and sticky mucus in the airways. This mucus can become a breeding ground for various bacteria, including *S. maltophilia*, making individuals with CF particularly susceptible to respiratory infections [6]. *S. maltophilia* is one of the opportunistic pathogens that can infect individuals with CF. CF patients are at risk of various bacterial and fungal infections due to the altered mucus environment in their airways. When *S. maltophilia* infects the respiratory tract of CF patients, it can cause symptoms such as increased coughing, difficulty breathing, and increased mucus production. These symptoms can exacerbate the already challenging respiratory issues in CF [37]. *S. maltophilia* infections in CF patients can sometimes become chronic, meaning that the bacteria persist in the airways for an extended period. Chronic infections can be challenging to treat and may require long-term antibiotic therapy. The treatment of *S. maltophilia* infections in CF patients typically involves the use of antibiotics. However, this bacterium is known for its resistance

to many commonly used antibiotics, including beta-lactams and aminoglycosides. Therefore, selecting the right antibiotic and monitoring the patient's response is crucial. Preventing *S. maltophilia* infections in CF patients involves maintaining good respiratory hygiene, adhering to prescribed therapies, and minimizing exposure to potential sources of infection. *S. maltophilia* has a natural resistance to many antibiotics and can acquire additional resistance through mutations and gene transfer mechanisms. This multidrug resistance can complicate treatment. Chronic infections, including those caused by *S. maltophilia*, can contribute to the progressive decline of lung function in individuals with CF. Managing and treating infections is a critical aspect of CF care to slow down this decline [38].

8. MALIGNANT TUMOR

This bacteria can cause infections in humans, particularly in individuals with compromised immune systems or underlying health conditions. While it is not typically associated with cancer directly. Cancer and cancer treatments, such as chemotherapy and radiation therapy, can weaken the immune system [39]. This weakened immune response can make cancer patients more susceptible to various infections, including those caused by *S. maltophilia*. It is considered an opportunistic pathogen, meaning it often infects individuals with weakened immune systems [40]. Cancer patients may be at an increased risk of acquiring infections from this bacterium due to their compromised immune function. *S. maltophilia* can cause respiratory tract infections, including pneumonia, in immunocompromised individuals. Cancer patients who are receiving treatments that affect the lungs or who have underlying lung conditions may be particularly vulnerable [6]. This bacteria is well known for its resistance to many antibiotics, which can complicate treatment in cancer patients already dealing with complex medical regimens. Careful consideration of antibiotic choice and possible multidrug resistance is essential when managing infections caused by this bacterium in cancer patients. Infections in cancer patients can have more severe consequences than in individuals with healthy immune systems. These infections can lead to delays in cancer treatments, hospitalizations, and increased morbidity and mortality rates. Preventing infections in cancer patients is crucial, and this often involves strict infection control measures, including careful hygiene, prophylactic antibiotics in some cases, and monitoring for signs of infection [41]. Early detection and prompt treatment are also essential. It's important to emphasize that *S. maltophilia* infections are relatively rare and primarily affect immunocompromised individuals [6]. Cancer patients should receive comprehensive care and guidance from their healthcare providers to minimize infection risks and manage any infections that may occur during their cancer treatment journey. The choice of antibiotics and treatment strategies should be tailored to the specific circumstances of the individual patient, taking into account their cancer type, treatment regimen, and overall health status.

9. HOSPITAL-ACQUIRED INFECTIONS

Hospital-acquired infections (HAIs), also known as nosocomial infections, pose a significant challenge to healthcare facilities worldwide. Among the many pathogens implicated in HAIs, *S. maltophilia* has emerged as an important and increasingly recognized causative agent. Hospital-acquired infections refer to infections that patients acquire during their stay in a healthcare facility, which were not present or in the incubation stage at the time of admission [41]. These infections can involve various microorganisms, including bacteria, viruses, fungi, and parasites. *S. maltophilia* is an emerging pathogen that has gained attention in recent years due to its association with HAIs. Understanding the role of this bacterium in nosocomial infections is crucial for effective prevention and management [42].

S. maltophilia is an environmental bacterium that can be found in water, soil, and on surfaces in healthcare settings. It has a remarkable ability to adapt to different environments and can survive on various surfaces, including medical equipment and devices [2]. This environmental resilience contributes to its prevalence in healthcare facilities. It is recognized as one of the leading non-fermentative gram-negative bacteria causing HAIs. It is frequently isolated from respiratory tract specimens, blood cultures, urinary tract samples, and wound swabs in hospitalized patients [43]. The infections with this bacterial species tend to affect patients with underlying health conditions or compromised immune systems. This includes individuals in intensive care units (ICUs), those receiving mechanical ventilation, patients with malignancies, transplant recipients, and individuals with chronic respiratory diseases [44]. *S. maltophilia* infections have been reported in healthcare settings, particularly in units with critically ill patients. Contaminated water sources, such as sink faucets and respiratory therapy equipment, have been identified as sources of outbreaks. Several factors increase the risk of acquiring *S. maltophilia* infections in the hospital setting such as, patients with weakened immune systems, such as those undergoing chemotherapy, organ transplantation, or long-term corticosteroid therapy, are at heightened risk [40]. ii, extended hospital stays, particularly in critical care units, increase the likelihood of exposure to the bacterium [44]. iii, The use of invasive medical devices, including central venous catheters, endotracheal tubes, and urinary catheters, provides potential entry points for infection [45]. iv, prior use of broad-spectrum antibiotics can disrupt the normal flora of the body, allowing opportunistic pathogens like *S. maltophilia* to thrive. v, Patients on mechanical ventilators, especially when used for an extended period, are at a higher risk of respiratory tract infections caused by this bacterium [46].

10. CONCLUSION

S. maltophilia is an opportunistic pathogens and sometime true pathogens according to the strains of bacteria. It responsible for several infectious diseases. It is also responsible for the high percentages of HAI. One of the attributes of this bacteria that makes it responsible for the wide board of infectious diseases is its resistance to a wide spectrum of antibiotics that is why the high mortality rate associated with infection with *S. maltophilia*. It was reported that following a special protocol of using more than of antibiotic in treating the infection with this bacteria is highly recommended by specialist physicians.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the ethical Committee of the University of Baghdad, Baghdad, Iraq (No 1014, 2020).

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