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Unraveling the complexity of *Stenotrophomonas maltophilia* – a comprehensive review of current knowledge

Review

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Abstract

Stenotrophomonas maltophilia is a Gram-negative (G-) opportunistic pathogen, prevalent and concerning for susceptible patients. It primarily causes nosocomial and some community-acquired respiratory and bloodstream infections. Reservoirs include water, plant rhizospheres, food, and animals. Virulence factors include motility, biofilm formation, and quorum sensing, with ongoing research on these mechanisms. A major concern is its multidrug resistance to antimicrobial agents like trimethoprim-sulfamethoxazole (TMP-SMX), β-lactams, macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and polymyxins. Effective treatments include TMP-SMX, quinolones, penicillins, and penicillins with β-lactamase inhibitors. Rapid diagnosis is crucial for successful treatment, leading to the development of new detection methods such as selective steno medium agar (SMA) and molecular techniques for nucleic acid detection. Patients with *S. maltophilia* are prone to co-infections with other G- bacteria. A study by Safdar et al. on cancer patients from 1986 to 2002 showed an increase in *S. maltophilia* infections from 2% to 7%, making it the 5th most commonly isolated G-bacterium in this group. It commonly infects ICU patients and individuals with SARS-CoV-2, with pneumonia being the most frequent clinical manifestation. The COVID-19 pandemic increased intensive care unit admissions and mechanical ventilation use, leading to higher infection rates of *S. maltophilia*.

Keywords

Stenotrophomonas maltophilia • antimicrobial resistance • biofilm • virulence factors • detection • treatment

1. Introduction

Stenotrophomonas maltophilia belongs to the domain *Bacteria*, within the phylum *Proteobacteria*, class *Gammaproteobacteria*, order *Xanthomonadales*, family *Xanthomonadaceae*, and genus *Stenotrophomonas*. The name "*Stenotrophomonas maltophilia*" is derived from a combination of Greek words: "*Stenos*", meaning narrow, "*Trophos*", indicating one who feeds or feeder, "*Monas*", denoting a unit, and "*Maltum*", referring to malt, along with "*Philia*", suggesting friendship [1]. This bacterium was originally isolated from pleural fluid by J.L. Edwards in 1943 and was named "*Bacterium bookeri*" [2]. After many years of discussion, in 1993, this bacterial strain was classified into the *Stenotrophomonas* genus as *S. maltophilia* by Paleroni and Bradbury [2,3]. Discovered in 1997 by Drancourt et al..[4] the bacterium *S. africana*, isolated from the cerebrospinal fluid of an *HIV*-positive Rwandan refugee, has been classified within the same genus as *S. maltophilia* due to its genetic resemblance.

2. Cytological and biochemical characteristics

A *S. maltophilia* bacterium appears as straight or slightly curved Gram-negative (G-) rods, typically measuring 0.5 to 1.5 µm in length. They are commonly found either individually or in pairs. These bacteria can thrive in nutrient-limited environments and possess polar flagella, which enable motility [5]. When grown in culture, these bacteria generate smooth, glossy colonies with consistent borders, varying in hue from white to pale yellow [6]. In a study conducted by Yinsai et al. [7] all out of 200 *S. maltophilia* strains tested positive for hemolysin production - 53% of strains produced α-hemolysin and 47% - β-hemolysin. *S. maltophilia* is classified as an obligate aerobe, capable of proliferation within a temperature range of 5 to 40°C, with optimal growth observed at 25°C. While the growth of the majority of *S. maltophilia* strains is contingent upon the availability of methionine or cysteine, certain strains do not require these amino acids for growth [8]. Complete genomes of *S. maltophilia* clinical strains – K279a, D457, ATCC 13637^T, MTCC 434^T, and STEN00241 have already been published [9,10,11,12,13]. Phage Salva, a novel *S. maltophilia* phage has a 60,789 base pairs (bp) genome containing 56,4% GC, one tRNA (transfer RNA), and 102 putative protein-coding genes [14]. The genome of *S. maltophilia* myophage Moby spans 159,365 base pairs (bp) and consists of double-stranded DNA with a GC content of 54.1%. It contains 271 predicted protein-coding genes

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and 24 predicted transfer RNA (tRNA) genes. [15]. Human bile was used to isolate the ZT1 strain of *S. maltophilia*. Following genome sequencing, a circular chromosome measuring 4,391,471 base pairs was discovered, containing 66,51% GC base pairs, 3962 protein-coding sequences, 7 rRNAs, and 74 tRNAs [16]. Various strains of *S. maltophilia* exhibit considerable genotypic and phenotypic heterogeneity, featuring strain-specific genes that are selectively expressed during adaptation to specific environmental niches. While different bacterial strains share a core genome, their pangenome is heterogeneous, encompassing genes that are variable across strains [6]. Phylogenetic analysis of 375 non-duplicated complex genomes of *S. maltophilia* strains of different origins demonstrated at least 20 genogroups [17]. *S. maltophilia* exhibits relatively low metabolic activity. It demonstrates positive results in the catalase test and the lysine decarboxylase test. The bacterium hydrolyzes esculin, gelatin, DNA, and polysorbate 80, while showing no activity in breaking down uric acid and starch. Glucose serves as the primary carbon source for *S. maltophilia*, although certain strains can utilize carbon from cellobiose, fructose, galactose, and mannose, with variability among strains ranging from 16% to 84%. Most strains yield negative results in the indole test, the ornithine decarboxylase test, the methyl red test, the sulfate reduction test, and the phenylalanine deaminase test. [5,18,19,20,21]. *S. maltophilia* exhibits resilience even in environments containing elevated concentrations of various heavy metals, including but not limited to copper, zinc, cobalt, nickel, mercury, silver, antimony, tellurite, selenite, lead, and molybdenum [21]. There is evidence suggesting that *S. maltophilia* has the capacity to acquire a repertoire of genes linked to antibiotic resistance and heavy metals from gram-positive (G+) bacteria such as *S. aureus* [22].

3. Virulence

Investigations into *S. maltophilia* have shown certain evidence of the virulence factors within this bacterial species. A nosocomial case of *S. maltophilia* bacteremia was reported by J.S. Brooke [5] in a patient with underlying leukemia and concomitant pyoderma gangrenosum. Due to the phenotypic similarities between pyodermas caused by *Pseudomonas aeruginosa* and *S. maltophilia,* a test for exoenzyme production by this bacterium was undertaken. Further analysis showed the production of large amounts of elastase and protease, which have been attributed to the pathogenesis of pyoderma [23]. In addition, a different strain of *S. maltophilia* obtained from another patient was tested for comparison. Analysis of the second strain revealed undetectable elastase activity and negligible protease production, suggesting inter-strain heterogeneity in elastase and protease expression among *S. maltophilia* [5,23]. In a later study by Thomas R [24], 108 different strains of *S. maltophilia* were tested and results showed that DNAse, gelatinase, hemolysin, hyaluronidase, lipase, and proteinase secretion occur in almost 100% of the tested strains, and heparinase and lecithinase secretion is present in most of them. A significant role in the spreading of this bacteria is its ability to adhere to different kinds of plastic, including intravenous cannulas and medical implants, which makes it capable of linear infections [23]. *S. maltophilia* also produces a biofilm composed of bacterial cells adhered to surfaces bound together by an extracellular matrix (ECM) containing proteins and polysaccharides [5]. Adhesion and penetration of *S. maltophilia* into airway epithelial cells have been investigated, revealing that the bacterium mainly attaches to intercellular junctions and only a negligible amount of the bacteria pervade inside the cells [25]. The virulence genes of *S. maltophilia* include protease enzymes *stmPr-1*, *stmPr-2*, esterase enzyme of *smlt3773* locus and genes associated with biofilm formation *smf-1*, *spgM*, *rmlA*, *rpfF* [14,26]. Serine proteases *stmPr1*, *stmPr2*, and *stmPr3* correlate with high cytotoxicity of *S. maltophilia* due to their ability to break up the ECM proteins of the host cell such as fibrinogen, type I collagen, and fibronectin [27]. These enzymes are linked to the degradation of IL-8, actin cytoskeleton alterations, cell separation, and loss of integrin/ECM linkages in mammals. As an outcome a cascade of caspases can be initiated, beginning with caspase 3, 6, and 7, which leads to apoptosis of the cell [27]. The *spgM* gene encodes enzymes phosphomannomutase and phosphoglucomutase which cause biosynthesis of thicker LPS (lipopolysaccharide) layer [28], the *rmlA* gene encodes an enzyme involved in LPS/EPS (exopolysaccharide)-coupled synthesis pathway, whereas the *rpfF* gene encodes diffusible signal factor (DSF) also known as cis-2-11-methyldodecenoic acid [15]. It was shown that DSF affected β-lactamase synthesis, rendering the bacterium resistant to β-lactam antibiotics [29]. *S. maltophilia* can stimulate peripheral blood mononuclear cells (PBMCs) to produce IFN-γ unlike other clinically common bacteria, TNF-α and IL-2. In addition, transmission electron microscopy (TEM) demonstrates that *S. maltophilia* enhances PBMC activation. Flow cytometry showed that *S. maltophilia* suppresses PBMC expression of CD4, CD8, CD69, CD147, and CD152 (CTLA-4). *S. maltophilia* activates the PD-1/PD-L1 signal pathway of PBMCs which can decrease T-cell activity and accelerate their apoptosis [25,30].

4. Symptoms

S. maltophilia infections often result from secondary infections by nosocomial pathogens, particularly prevalent among ICU patients. *S. maltophilia* primarily incites bloodstream and pulmonary infections. Symptoms of bloodstream infection typically encompass systemic manifestations such as fever, tachycardia, hypotension, nausea, vomiting, and diarrhea [31]. Patients experiencing pulmonary infection often manifest symptoms such as coughing, dyspnea, chest discomfort, and fever. Radiographic evaluations commonly reveal lung infiltrates with lobular patterns or distinctive pleural effusions [32].

5. Epidemiology

S. maltophilia exhibits presence in environmental reservoirs including freshwater aquatic ecosystems (lakes and rivers), the plant rhizosphere, and various unprocessed foodstuffs (salads, raw milk, and frozen fish) [6, 33, 34]. Nosocomial colonization of *S. maltophilia* is observed through a wide range of medical devices and equipment, including respiratory circuits, endoscopes, intravenous fluids, catheters, blood collection tubes containing ethylenediaminetetraacetic acid (EDTA), dialysis machines, intra-aortic balloon pumps, nebulizers, oxygen humidifiers, hospital tap water faucets, sinks, and shower outlets. Notably, colonization of disinfectant solutions also occurs, highlighting its potential role in transmission. This extensive repertoire of colonized medical equipment underscores the significant risk posed by *S. maltophilia* in healthcare settings [6, 33, 34]. Risk factors for developing a *S. maltophilia* infection include hematological malignancies, neutropenia, thrombocytopenia, underlying malignancy, chronic respiratory disease, immunosuppressive conditions, and septic shock. Hospital-connected risk factors include prolonged hospitalization, mechanical ventilation for greater than seven days or tracheostomy, central venous catheter (CVC) or other foreign bodies, mucosal damage such as that which occurs with chemotherapy or radiation, prolonged antibiotic use, and admission to the ICU [1,6,33,35]. *S. maltophilia* is primarily associated with respiratory tract infections but is also often found in the oropharyngeal microbiome of hospitalized patients and patients with cystic fibrosis, while it is rarely found in the oropharynx of healthy patients [6,36]. The pathogen can induce infections such as opportunistic infections including bacteremia, pulmonary infections, urinary tract infections, skin and soft tissue infections (SSTI), gastrointestinal tract infections, liver infections, nervous system infections, bone infections, medical implant infections, as well as meningitis and endocarditis [37,38,39,40]. *S. maltophilia* infections present distinct patterns in adult and pediatric patients. While adults often experience these infections as secondary or co-infections, pediatric patients primarily encounter them as the primary infection. This discrepancy in infection types is attributed to underlying pathologies such as malignancy, congenital heart disease, anemia, and primary immunodeficiency prevalent in pediatric cases [41,42].

6. Detection

A diverse array of material serves as reservoirs used in testing for *S. maltophilia* presence, including catheters, endoscopes, hemodialyzers, water sources, ventilators, heater-cooler units, dental plaque biofilms, and contact lenses. The observed upsurge in *S. maltophilia* prevalence coupled with its heightened antibiotic resistance underscores the importance of implementing rapid diagnostic methods for infections caused by this opportunistic pathogen. Recent advancements have yielded novel methodologies for the detection of *S. maltophilia.* Blood culture colonies of *S. maltophilia* usually appear yellow-green when cultured on nutrient agar. On blood agar, they are non-hemolytic with a faint lavender hue and emit an ammonia odor. On MacConkey plates, they remain colorless due to their inability to ferment lactose [33]. In a study by Goncalves-Vidigal et al. [36], Steno medium agar (SMA) was used to isolate the bacteria from sputum and showed an increased detection rate in comparison to conventional media. SMA is relatively easy to produce and does not require extensive processing of sputum to culture examined strain. However, because of the gradual degradation of imipenem used to produce this medium, it can only be used for 3 weeks after production is completed [36]. DNase activity in *S. maltophilia* strains can be used to differentiate them from other nonfermenting G- bacteria with the use of a modified DNase tube test (MDTT) which showed positive results in various clinical samples such as pus, urine, and tracheal aspirate [43]. This method needs only 6h of incubation time which allows for faster diagnosis in comparison to the classical DNase tube test which needed up to 96h to reach similar sensitivity [43,44]. These methods allow only for preliminary identification of *S. maltophilia,* and more testing is required to confirm the identification of this pathogen.

To detect *S. maltophilia* in polymicrobial infections, nucleic acid detection methods are being developed [45,46]. RT-PCR (reverse transcription – polymerase chain reaction) is used to detect an amplicon specific to *S. maltophilia*. It consists of 344 base pairs and spans the coordinates 3,935,993 to 3,936,336 within the K279a genome, precisely situated within the *fdnG* gene. This method is precise enough to differentiate *S. maltophilia* and *S. indicatrix* based on differences in their RS7 region [47]. RT-PCR can also be used to detect mutated genes *smeRv* and *smeT*, which regulate efflux pumps responsible for *S. maltophili* a resistance to TMP-SMX (trimethoprim-sulfamethoxazole) [48], and the mutated *smeDEF* gene responsible for fluoroquinolone resistance [49]. *S. maltophilia* resistance genes *sul1*, *sul2,* and *blaL1* can be detected using both PCR and loop-mediated isothermal amplification (LAMP) techniques. However, the LAMP method exhibited ten times higher specificity compared to PCR [50,51]. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) can be used to identify *S. maltophilia* from samples prepared directly from biofilm. This method enables the rapid identification of the infection's etiological agent, facilitating the early initiation of appropriate antibiotic therapy [52]. The limitation of this method is that biofilm samples may not possess an adequate concentration of bacterial cells to produce a detectable mass spectrum [53]. A study by N. Hansen et al. [46] showed how the usage of novel peptide nucleic acid probe (PNA) in fluorescent in-situ hybridization (FISH) can provide better sensitivity and specificity along with possibilities to detect *S. maltophilia* in mixed populations and faster completion of the test. Next generation sequencing of cell-free DNA (NGS of cfDNA) is another method that can be

Table 1. Summary of studies investigating antibiotic resistance of S. maltophilia

Authors	Year	Antibiotic resistance findings
Rahmati-Bahram et al. [81]	1996	Investigated temperature-dependent aminoglycoside resistance in *S. maltophilia*, highlighting alterations in protein and lipopolysaccharide with growth temperature.
Avison et al. [76]	2000	Identified a TEM-2 -lactamase encoded on an active transposon in the genome of a clinical isolate of *S. maltophilia*.
Barbier-Frebour et al. [77]	2000	Explored the molecular mechanisms behind the rapid emergence of ticarcillin-clavulanate resistance in *S. maltophilia* isolates.
Zhang et al. [79]	2000	Involvement of a multidrug efflux system in multiple antibiotic resistance in *S. maltophilia.*
Alonso and Martínez [75]	2000	Cloning and characterization of SmeDEF, a multidrug efflux pump from *S. maltophilia*
Avison et al. [70]	2001	Plasmid location and molecular heterogeneity of beta-lactamase genes of *S. maltophilia.*
Poole [74]	2004	Efflux-mediated multiresistance in Gram-negative (G-) bacteria, including mechanisms in *S. maltophilia.*
Gülmez and Hasçelik [71]	2005	Antimicrobial resistance and molecular typing of *S. maltophilia* in a Turkish university hospital
Toleman et al. [78]	2007	Global emergence of trimethoprim/sulfamethoxazole resistance mediated by acquisition of *sul* genes in *S. maltophilia.*
Valenza et al. [80]	2008	Prevalence and antimicrobial susceptibility of microorganisms, including *S. maltophilia*, isolated from patients with cystic fibrosis.
Liaw et al. [72]	2010	Multidrug resistance in clinical isolates of *S. maltophilia*, including roles of integrons, efflux pumps, and biofilm formation.
Al Johani et al. [69]	2010	Prevalence of antimicrobial resistance among G- isolates in an adult intensive care unit, including *S. maltophilia.*
Hu et al. [82]	2011	*S. maltophilia* resistance to trimethoprim/sulfamethoxazole mediated by acquisition of *sul* and *dfrA* genes in a plasmid-mediated class 1 integron.

used to diagnose patients with an *S. maltophilia* infection [54]. Results from NGS of cfDNA technology must be interpreted carefully and compared with other diagnostic findings since there is a possibility to detect patient's commensal microbiota aside from bacteria that cause infection [55]. The main limitation of molecular detection methods is their inability to differentiate between live and dead cells. However, they provide relatively quick results with high sensitivity and specificity which allows one to choose an appropriate treatment without having to wait for identification using conventional methods.

7. Treatment

A study by Chang L.L. et al. [56] conducted on a group of 759 patients showed similar results of superinfections during treatment with imipenem and ceftazidime. TMP-SMX was the preferred treatment according to references [57,58]. Notably, between 2004 and 2009, clinical isolates of *S. maltophilia* obtained from an adult tertiary care center in Saudi Arabia exhibited a significant increase in gentamicin resistance, while 90% of the isolates remained susceptible to TMP-SMX [59]. Additionally, antibiotic susceptibility testing conducted by Barbolla R et al. [60] on 66 *S. maltophilia* clinical isolates from two university hospitals in Rouen, France, and Tunis, Tunisia, collected between 1994 and 1997, revealed a gradual rise in ticarcillin-clavulanate resistance percentages from 19% (1995) to 32% (1996) to 42% (1997). It is noteworthy that the concurrent administration of TMP-SMX with either ticarcillin/clavulanate or a third-generation cephalosporin is advised for patients experiencing neutropenia or severe illness, as delineated in a study by Kataoka D et al. [61]. Cefiderocol, an innovative injectable siderophore cephalosporin, penetrates the outer cell membrane by emulating a natural siderophore. This mechanism disrupts the biosynthesis of G- bacterial cell walls. Its efficacy against *S. maltophilia in vitro* is attributed to its efficient translocation across the outer cell membrane and its resistance to both serine and metallo-β-lactamases [62,63,64,65]. B. Behera's study suggests that cefiderocol may have significant clinical utility, demonstrating complete *in vitro* effectiveness against all tested *S. maltophilia* isolates. However, clinical trials have yet to be conducted to confirm these findings [62,66]. A currently ongoing clinical study is investigating lung transplant patients who have undergone prophylactic treatment for *P. jiroveci* infection. Researchers aim to compare the clinical and microbiological outcomes of these patients and evaluate the resistance of *S. maltophilia* to TMP-SMX, based on the prophylactic regimens administered [67]. In another clinical trial, investigators aim to compare the clinical outcomes and failure rates of standard versus alternative treatments for *S. maltophilia* infections. These treatments include minocycline, moxifloxacin, ciprofloxacin, or ceftazidime, either as monotherapy or in combination with TMP-SMX, alternative TMP-SMX dosing regimens, and varying therapy durations [68]. A summary of studies regarding antibiotic resistance in *S. maltophilia* is described in Table 1.

8. Antibiotic resistance

S. maltophilia is known for its resistance to a wide array of antibiotics, including TMP-SMX, β-lactams such as carbapenems and cephalosporins, macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and polymyxins. *S. maltophilia* develops resistance through specific bacteria characteristics such as low membrane permeability for antibiotics and efflux pumps [69,70,71,72,73,74], β-lactamases [74,75,76,77,78], and drug-modifying enzymes. The existence of antibiotics in the environment can promote the growth of antibiotic-resistant bacteria, consequently raising the chances of other bacteria developing resistance to drugs. This occurs through mechanisms such as plasmids, transposons, integrons, integron-like elements, biofilms, and insertion element common region (ISCR) [72,76,77,80,81]. A study by A. Rahmati-Bahram et al. [81] observed variations in the sensitivity of *S. maltophilia* to aminoglycosides at different temperatures. Additionally, differences in resistance rates were noted when assessed after 24 and 48 hours of incubation. Significant differences were particularly noted in the efficacy of TMP-SMX, ciprofloxacin, ceftazidime, cefepime, piperacillin, and piperacillin-tazobactam [82]. Based on samples obtained from patients with cystic fibrosis (CF) and those without the condition, it was shown that bacterial strains are more resistant in isolates from patients in the first group. The study included piperacillin, cefotaxime, cefepime, moxalactam, ciprofloxacin, ofloxacin, sparfloxacin, gatifloxacin, and doxycycline. In 2006, research led by G. Valenza et al. [80] investigated *S. maltophilia* strains isolated from sputum samples of CF patients at a large German hospital. The results indicated that only 34.4% of the strains were susceptible to TMP-SMX, 25% were susceptible to ciprofloxacin, and all strains exhibited resistance to imipenem.

9. Conclusions

S. maltophilia is an opportunistic pathogen posing a serious threat to vulnerable patient populations. This can be particularly dangerous for patients with lowered immunity or lung diseases.

Bacterial resistance to previously used treatments is increasing. The COVID-19 pandemic has increased the number of intensive care patients treated with mechanical ventilation, resulting in a rise in *S. maltophilia* infections, which can increase patient mortality through bacteremia. Therefore, it is crucial to introduce novel, rapid methods to diagnose *S. maltophilia* infections and provide the infected patients with accurate and specific treatment.

Given the growing significance of this pathogen and the often serious clinical consequences of infection, knowledge about the virulence factors and the local and global transmission of *S. maltophilia* should be expanded.

Authors' contribution

M.S. and M.C. were responsible for the conception and design of the publication. B.N., B.O. were responsible for the acquisition of the literature for the manuscript. B.N., B.O. wrote the original draft of the manuscript; M.S., B.N., and B.O. reviewed and edited the manuscript; M.C. supervised the paper. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors have no potential conflict of interest to declare.

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