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Review

Stenotrophomonas maltophilia and Its Ability to Form Biofilms

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Abstract: In the last ten years, *Stenotrophomonas maltophilia* has gained increasing interest as an important agent of infection, which is why it has come to be recognized as a serious cause of nosocomial infections related to bloodstream infections, pneumonia, and cancer, mainly in patients with intensive care, and is associated with high mortality rates in immunocompromised patients, with prolonged hospital stays and extensive use of antimicrobials. The importance of this microorganism lies in its low pathogenicity, high multiresistance to various antibiotics, and frequent and persistent isolation in predisposed patients. In addition, few studies have evaluated its epidemiology and clinical relevance. The pathogenesis of biofilms lies mainly in the fact that they can generate persistent chronic infections that are difficult to eradicate. To this extent, it is important to make the characteristics of the biofilm formation behavior of *Stenotrophomonas maltophilia* known and generate more knowledge about its colonization or infection in humans through this review, which discusses more recent information.

Keywords: *Stenotrophomonas maltophilia*; biofilm; emerging bacteria; multiresistant

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1. Introduction

An important virulence factor in bacterial microorganisms is the ability to form biofilms, and a significant number of cellular- and extracellular-associated virulence factors in *S. maltophilia* are involved in colonization and biofilm formation on host surfaces [1]. Biofilms are complex communities of microorganisms attached to a surface that is held together by self-produced polymeric matrixes made up of proteins, extracellular deoxyribonucleic acid (DNA), and exopolysaccharides (EPS) [2].

Although *S. maltophilia* is a pathogen with low virulence, the ability to form biofilms on various biotic and abiotic surfaces is an important virulence characteristic, and the same biofilm formation process is shared by most bacteria, consisting of three key stages. The first stage spans from the first 30 min to 1 h and requires planktonic cells to adhere by weak interaction to a surface. Semiflexible peritrichous fimbriae and long, thick flagella filaments aid biofilm formation by promoting attachment to the surface. After 4 h, the second stage begins, with irreversible cell attachment mediated by flagella, pili, and other surface appendages. These multilayered cells accumulate by subdivision and initiate self-production of a matrix of extracellular polymeric substances (EPS) after a lapse of 10 h, ensuring the attachment of bacteria to the surface and the assembly of cells to form microcolonies. Finally, the third stage begins at 18 h and reaches its maximum intensity at 24 h, in which the differentiation of the biofilm occurs in a mature structure that contains small water channels, which help to transport nutrients, water, and debris and allow signaling molecules to be distributed effectively within the biofilm. Once the biofilm reaches a mature stage, the biofilm cells separate individually or in groups, releasing planktonic bacteria into the environment, which spread and colonize other niches through swimming motility [3].

Stenotrophomonas maltophilia is an opportunistic, multiresistant nosocomial pathogen with an increasing prevalence and high morbidity and mortality that requires more specific treatment due to its high antimicrobial resistance profiles [4,5].

It is a ubiquitous organism because it has a broad ecological distribution found in diverse anthropogenic and natural settings associated with humans, animals, and plants [6]. It causes difficult-to-treat infections [7] that lead to increased morbidity and mortality, especially in immunocompromised patients with prolonged hospital stays and who have received long-acting antimicrobials [8]. To this extent, it is important to have a better understanding of the mechanisms involved in the biofilm formation capacity of *S. maltophilia* through this review, which discusses more recent information. That helps the production of new research on it, contributing to finding new alternatives that allow the discovery of both mechanisms that violate its resistance capacity, as well as treatments that have greater efficacy against this multiresistant pathogen that mainly affects immunocompromised patients and cancer patients in treatment with chemotherapy and immunosuppressive treatments.

2. Virulence Factors

S. maltophilia has been classified as a microorganism of limited pathogenicity due to the difficult task of differentiating cases of colonization from cases of infection. In addition, virulence factors, as well as other cellular and molecular mechanisms that are known to be involved in infectious pathogenesis, have yet to be studied in detail [9].

Despite this, some virulence factors involved in the pathogenicity of *S. maltophilia* are known and are divided into extracellular virulence factors and cell-associated virulence factors. Within the extracellular virulence factors are nucleases (DNase and RNases), proteases (StmPr1, StmPr2, StmPr3, StmPr4, gelatinases, elastase, and fibrinolysin/streptokinase), lipases (lipase and phospholipase C and D), siderophores, esterases, hyaluronidases, heparinases, hemolysins, and cytotoxins. Cell-associated virulence factors include lipopolysaccharides, pilis or fimbriae (SMF-1, type IV pilus machinery), nonpilis adhesins (nonfimbrial), and flagella. Other factors involved are biofilm formation factors (phosphoglucomutase/phosphomannose bifunctional protein, glucose-1-phosphate thymilyltransferase, biofilm and swimming motility regulator, outer membrane protein Ax21), polysaccharide lyase, nitrate reductase, *RpfC* and *rpfF* regulators, hemagglutinin, and the Xps type II secretion system [9,10].

2.1. Proteases

Proteases are believed to play an essential role in bacterial pathogenesis, as they are involved in tissue invasion and damage [11]. Some genetic factors discovered so far that possibly contribute to the virulence of *S. maltophilia* are the genes for the StmPr1 protease and the SMF-1 fimbrial operon. Four extracellular serine proteases called StmPr1, StmPr2, StmPr3, and StmPr4 have been found and have been identified as detergent proteases, and although the four proteases differ significantly in primary structure, they share common features, such as the presence of a signal sequence, a pro sequence, and a C-terminal domain in StmPr1, StmPr2, and StmPr3, like some peptidases secreted by bacteria. Although extracellular serine proteases are considered important pathogenic factors, extracellular proteases from *S. maltophilia* are poorly characterized in the literature. Only the major extracellular protease StmPr1, derived from an immunocompromised patient sample, has been well-characterized and shown to be capable of degrading several human serum and connective tissue proteins [11]. It is an endopeptidase with broad substrate specificity that works best at pH 9.0 and is considered a relevant virulence factor of *S. maltophilia* [12], as it contributes to *S. maltophilia*-mediated inflammation in the lung and degrades collagen and fibronectin in lung epithelial cells [13]. Additionally, StmPr1 and StmPr3, which are present in *S. maltophilia* sequencing, contribute to the overall virulence potential [11,14]. It is known that StmPr3 has an optimum pH of 12, which is considered extremely high; as for StmPr2, its sequence has been determined, and for StmPr4, there is still no information available [11,15].

2.2. Flagella

Flagella are highly immunogenic structures conserved among clinical isolates of *S. maltophilia* and that participate not only as adhesion mediators but also as chemotactic factors involved in biofilm formation [14]. Flagella are well-characterized in various Gram-negative bacteria such as Escherichia coli, Vibrio cholerae, and Pseudomonas aeruginosa, but little is known about these aspects of *S. maltophilia*. However, it has been possible to observe that most of the 59 genes involved in the biosynthesis of flagella in *P. aeruginosa* are conserved in the *S. maltophilia* genome [16]. Furthermore, it should be noted that the flagellin of *S. maltophilia* may be crucial in the development of an inhibitor that allows limited swimming, adhesion, and formation of flagella-mediated biofilms [17], since studies have been carried out that corroborate the participation of *S. maltophilia* flagellin as a bacterial adhesin in tracheal mucus in an animal model, which explained that binding to mucus is carried out through the flagella and that this binding can hinder the movement of organisms in the respiratory tract, indirectly influencing the establishment of *S. maltophilia*, and, therefore, the formation of biofilms attached to the flagella may also protect *S. maltophilia* from the host's immune response [18].

2.3. Pilis

Fimbriae are an essential structure present in the adhesion process. Adherence to epithelial cells and biofilm formation is mediated by these fibrillar structures, called fimbriae or pili, composed of several thousand monomeric fimbrins or pilin subunits. It has been described that its primary function is to act as a bridge between the bacteria and the surfaces to which they adhere, whether inert surfaces or epithelial cells [19].

In clinical strains of *S. maltophilia*, type 1 fimbriae (SMF-1) have been characterized, and they are semiflexible peritrichous fimbriae that measure 5–7 nm and form at 37 °C [19]. SMF-1 fimbrin is closely related to some families of fimbrial adhesins such as F17 (human and animal pathogenic *E. coli*), K99 (enterotoxigenic animal *E. coli*, ETEC), G fimbriae (uropathogenic *E. coli*, UPEC), 20K fimbriae (bovine *E. coli* C31A), and CupA (*P. aeruginosa*). It is understood that these families of fimbriae extended to the genus Stenotrophomonas, a genetically distant bacterial genus, with a percentage of identity between the amino N-terminal region of *SMF-1* with the N-terminals of the other families of fimbriae around it from 50 to 61% [14,20].

This *SMF-1* fimbrial operon includes Smlt0706-Smlt0709 [21]. It is composed of a 17-kDa fimbrin subunit, which shares significant similarities with the N-terminal amino acid sequences of several fimbrial adhesins found in pathogenic strains of *Escherichia coli*. Adherence and biofilm formation on *S. maltophilia* surfaces are inhibited by the presence of anti-*SMF-1* antibodies, corroborating the interaction between these fimbriae, the *S. maltophilia* surface, and the surface of the host cell. Consequently, *SMF-1* fimbriae are involved in hemagglutination, biofilm formation, and adhesion to cultured mammalian cells [14]. It is worth mentioning that the fimbrin SMF-1 of *S. maltophilia* stimulates the local innate immune response, characterized by a high production of proinflammatory cytokines, chemokines, and nitric oxide. In addition, it increases the infiltration of neutrophils and the capacity of bladder epithelial cells to engulf and kill bacteria in vitro [22]. Gallo et al. (2016) found the *SMF-1* gene in 23% of the clinical isolates and 42% from the hospital environment and medical devices and associated the presence of the gene that encodes the SMF-1 fimbriae in *S. maltophilia* with the production of biofilms; practically 97% of the isolates that expressed the *SMF-1* gene could form biofilms to different degrees: 48.4% produced weak biofilms, 45.2% moderated, and 3.2% formed strong biofilms. Additionally, they stated that *SMF-1* is not detected in plasmids because this gene has not been mobilized from the chromosome [23]. Azimi et al. (2020) also mention that due to a high prevalence of the *SMF-1* gene (99.3%), a significant relationship was found between the *SMF-1* gene and the ability to form biofilms ($p = 0.018$) [24].

Adamek et al. (2014) compared the virulence genes of clinical strains (amoeba virulent SKK35 and amoeba avirulent K279a) and environmental strains (three amoeba avirulent

strains, RA8, R511-3, and SKK35) of *S. maltophilia*, revealing that the genome sequence of each strain contains a list of genes that contribute to virulence potential. Within these genes, those with adhesion and motility factors were found, as is the case of the fimbrial protein *SMF-1*, which showed minor variations in different phenotypes of *S. maltophilia* that could play a role in the colonization capacity, especially in the host, leading to biofilm formation on invasive devices, surface adhesion, and other types of interfaces. The homologous regions found of the fimbrial protein *SMF-1* were conserved regions present in all *S. maltophilia* strains: K279a (706), R5513 (561), SKA14 (3834), RA8 (769), and SKK35 (2843) [25].

Another type of pili important to mention, called type IV pili, are unique for their multifunctionality and ubiquity. They present flexible filaments of 4–8 nm in diameter [26], several μm long (approximately 1000 times longer than they are wide) [27], and polymers of one major type IV pilin that are assembled by conserved multiprotein machineries [26]. The core proteins of the type IV pili in Gram-negative bacteria are composed of a major pilin subunit, a prepilin peptidase, an assembly ATPase, an inner membrane core protein, and an outer membrane secretin channel [28].

According to their characteristics, type IV pilins are divided into two subclasses: type IVa and type IVb. Type IVa pilins have a short leader sequence of 5–6 amino acids and a mature sequence of 150 amino acids, the N-terminal N-methylated residue is phenylalanine, and they occur in a wide variety of Gram-negative bacteria with a wide diversity of hosts such as mammals, including humans, plants, fungi, etc. Type IVb pilins have a leader sequence of 15–30 amino acids and a mature sequence of 190 amino acids, and the N-terminal N-methylated residue can vary between methionine, leucine, or valine, being identified exclusively in bacteria that colonize the human intestine [29].

Type IV pili have been proposed to function as mechanical sensors to rapidly signal contact with the surface [30], since their polymeric structure allows it to mediate a variety of cellular functions, including microcolony and biofilm formation, surface motility, adhesion to host cells, cell signaling, DNA uptake by natural transformation, and their participation as receptors for bacteriophages [29,31]. Many of these functions, including surface motility, chemotaxis, phototaxis, and regulation of biofilm structure, may require large forces and high velocities that are supported by retraction ATPases [32].

Regarding *S. maltophilia*, Kalidasan and Neela (2020) proposed a model of type IV pili in this pathogen based on studies of *P. aeruginosa*, whose structure is composed of a major pilin (PilA/PilE), a secretin PilQ, alignment proteins (PilM, PilN, PilO, PilP), a retraction ATPase (PilT), an assembly ATPase (PilB), and minor pilins (PilX, PilW, PilV). In addition, the contraction motility of *S. maltophilia* is mediated by these type IV pili found at one or both poles of the cells [19]. However, despite the reported works, the role of type IV pili in virulence has yet to be studied in depth in *S. maltophilia* [33]. Nevertheless, they are considered key virulence factors in various human pathogens that lead to infections that increase morbidity and mortality rates worldwide, making it a primary issue for decades [27].

3. Biofilm on Inert Surfaces

S. maltophilia has a positive surface charge at physiological pH, which favors its adherence to negatively charged materials such as Teflon and glass. As part of its ability to firmly adhere to different types of plastics, mainly in hospital environments, it allows this infection/colonization process to be associated with contamination of surgical material, as well as catheterization, intubation, and tracheotomy techniques, by use of intravascular cannulas and endotracheal tubes, among others [34–36]. For example, patients with alloplastic orthopedic devices develop 1.5–2.5% of infections due to primary intervention and up to 20% during revision procedures [37]. Therefore, the formation of tightly adhered biofilms may be associated with their isolation from device-associated infections [38]. Hydrophobicity is also known to be related to adhesion and biofilm formation on polystyrene surfaces, and this ability is highly conserved in *S. maltophilia* [39].

The biofilms formed by *S. maltophilia* are a recognized feature of this pathogen despite their clinical relevance being not yet fully understood. However, the biofilm-forming ability of *S. maltophilia* is highly conserved even though there are variations between strains. In addition, the ability to form biofilms is greater in strains that cause infections in the hospital environment. Therefore, it is stated that the ability to produce biofilms is considered a determinant of the virulence ability of *S. maltophilia* and supports the role of biofilm formation in the establishment of infection [40].

ElBaradei and Yakout (2022) evaluated the effect of ascorbic acid on the formation of *S. maltophilia* biofilms in one of the first studies to evaluate this effect. It is a non-chemotherapeutic alternative that hinders biofilm formation without causing antimicrobial resistance, demonstrating that ascorbic acid can inhibit *S. maltophilia* biofilm formation in a concentration-dependent manner, and it did not form biofilms at sublethal doses. The highest percentage of inhibition of biofilms could be observed using the minimum inhibitory concentration (MIC) with values that ranged between 0.78 and 50 mg/mL. The MIC 50 and MIC 90 were 3.125 mg/mL and 6.25 mg/mL, respectively [41].

Pandit et al. (2017) propose that this inhibitory effect of ascorbic acid on the formation of biofilms is due to the inhibition of quorum detection, among other mechanisms involved in the development of biofilms that allow, as a consequence, the inhibition of biosynthesis of polysaccharides, thus reducing the content of extracellular polymeric substances; at concentrations of 30 mM ascorbic acid, the bacterial cells are entirely exposed to the medium, being more susceptible to death due to oxidative stress induced by the acid ascorbic [42].

4. Antibiotic Resistance

As is already known, *S. maltophilia* is a highly multidrug-resistant pathogen due to its intrinsic and acquired resistance properties to a wide range of antibiotics and chemotherapeutic agents [43,44], with a wide range of resistance determinants that are responsible for its low sensitivity phenotype. In addition, bacterial exposure to antibiotics results in variations in bacterial physiology that are associated with modifications in bacterial transcription, where some of these changes are an indirect consequence of the presence of antimicrobials and others are related to the expression of genes related to antibiotic stress that allows maintaining homeostasis in the presence of the antibiotic [45].

S. maltophilia is intrinsically resistant to practically all commonly used antibiotics, including antipseudomonal drugs, aminoglycosides, and carbapenems; it has proven susceptibility, and the dilemma of in vitro susceptibility testing poses a great challenge when selecting an antimicrobial regimen suitable for the treatment of *S. maltophilia* infections [46]. Furthermore, it can acquire new resistances through the horizontal transfer of genes and mutations [47]. Therefore, correct identification of antimicrobials is important since no drug is widely effective against this pathogen, and, consequently, the initiation of adequate treatment is difficult, triggering an increase in morbidity and mortality.

Although there are differences between countries and continents, in recent years, an increase in nosocomial infections caused by *S. maltophilia* strains has been reported worldwide, with an increasing trend from 1.3% to 1.7% between 1997 and 2012 [7]. Other studies indicate that the prevalence of *S. maltophilia* associated mainly with respiratory tract infections ranges from 1.6–6.3% [48], for intra-abdominal infections ranging from 1 to 1.7% [49], and countries in Africa and the Middle East report unusual isolation rates of urinary tract infections, likewise, China reports isolation rates of 1.3% and Thailand 3.3% [50]. It has also been reported that in patients with *S. maltophilia* bacteremia, the mortality rate is 65.1%, with independent risk factors associated with hypoalbuminemia, hematologic malignancy, and quinolone-resistant strains [51].

Trimethoprim/sulfamethoxazole (TMP/SMX) remains the primary antimicrobial drug of choice for the treatment of *S. maltophilia* infections [52], as it has been shown to have sensitivity rates of 62.5% to 100% [38,53–58] (Table 1). However, in the last ten years, greater resistance to TMP/SMX has been observed, with rates reported from 2.3% to

77% [4,17,38,51,53,55,57–64]; despite this, most studies worldwide show that *S. maltophilia* continues to be highly susceptible [43].

Table 1. Antimicrobial resistance and susceptibility rates of *S. maltophilia*.

Country	Year	Nunber of Isolates	Resistance to Antibiotics (%)	Sensitivity to Antibiotics (%)	References
China	2010–2012	426	Minocycline (0.5%), levofloxacin (3.3%), Tmp/Smx (74.3%)		[59]
China	2005–2014	300	Tmp/Smx (38.7%)		[60]
Egypt	2013–2015	32	Tigecycline (0%), Colistin (15.6%), Levofloxacin (18.7%), Tmp/Smx (37.5%), Ticarcillin Clavulinic Acid (37.5%), Ceftazidime (37.5%), Pipracillin/Tazobactam (47%), Ciprofloxacin (53%), Amikacin (59.4%), Gentamicin (59.4%), Imipenem (100%)	Tigecycline (100%), Colistin (84.4%), Levofloxacin (81.2%), Tmp/Smx (62.5%), Ticarcillin Clavulinic Acid (62.5%), Ceftazidime (62.5%), Pipracillin/Tazobactam (53%), Ciprofloxacin (47%), Amikacin (40.6%), Gentamicin (40.6%), Imipenem (0%)	[53]
Italy	2003–2014	91	Ceftazidime (86.6%), Piperacillin/Tazobactam (85.5%), Amikacin (62%)	Minocycline (98.9%), Doxycycline (94.6%), Tmp/Smx (93.4%)	[54]
Mexico	2007–2015	196	Meropenem (93.4%), Gentamicin (55.1%), Ceftazidime (52.3%), Cefotaxime (51.5%), Amikacin (42.3%), Cefepime (32.1%), Ciprofloxacin (26%), Tmp/Smx (25%), Chloramphenicol (14.3%), Levofloxacin (2.6%)		[61]
Argentina	2004–2012	63	Ciprofloxacin (23.8%), Levofloxacin (9.5%) Tmp/Smx (6.3%)	Tmp/Smx (93.6%), Levofloxacin (85.7%), Ciprofloxacin (58.7%)	[38]
Iran	2015–2016	44		Tmp/Smx (100%), Colistin (100%), Ceftazidime (93.2%) Ciprofloxacin (84.1%)	[55]
South Korea	2006–2015	126 bacterium	Quinolone (31.2%), Tmp/Smx (11.9%)		[51]

Table 1. *Cont.*

Country	Year	Nunber of Isolates	Resistance to Antibiotics (%)	Sensitivity to Antibiotics (%)	References
Iran	2016–2017	150	Imipenem (>94%), Meropenem (>94%), Aztreonam (>94%), Cefepime (52.7%), Ceftazidime (43.3%), Chloramphenicol (43.3%), Colistin (41.3%), Tigecycline (30%), Piperacillin/Tazobactam (25%), Gentamicin (22%), Tmp/Smx (20.7%), Doxycycline (10%), Ticarcillin/Clavulanate (8.7%), Ciprofloxacin (9.3%), Levofloxacin (1.3%), Minocycline (1.3%)		[24]
Mexico	2016–2017	30	Tetraciclina (80%), Tmp/Smx (76.6%), BLEE (23.3%)	All antibiotics (10%)	[43]
China	2014	93	Levofloxacin (4.3%), Tmp/Smx (9.7%)	Minocycline (100%)	[62]
Hungary	2008–2017	817	Amikacin (72.5%)	Colistin (92.2%), Levofloxacin (90.5%), Tigecycline (90.5%), Tmp/Smx (87.4%)	[56]
Iran	2017–2018	117	Chloramphenicol (27.1%), Ceftazidime (27.1%), Minocyclin (16.1%), Tmp/Smx (10.2%)		[63]
Iran	2018–2019	85	Imipenem (100%), Meropenem (100%), Doripenem (100%), Ceftazidime (75.7%), Levofloxacin (4.7%), Tmp/Smx (2.3%)	Minocycline (100%), Tmp/Smx (97.6%), Levofloxacin (95.2%)	[57]
Iraq	2016–2020	3569	Ceftazidime (100%), Chloramphenicol (100%), Ciprofloxacin (93%), Cefepime (93%), Evofloxacin (92%), Aztreonam (84%), Ticarcillin-Clavulanic Acid (83%), Minocycline (81%), Imipenem (45%), Tmp/Smx (77%), Gentamicin (70%), Azithromycin (56%), Fosfomycin (34%), Nitrofurantoin (22%)		[64]
United States	2015–2018	325	Tmp/Smx (6.8%), Levofloxacin (6.8%)	Tmp/Smx (87%), Levofloxacin (84%), Ceftazidime (39%)	[58]
Taiwan	2014–2016	1213	Levofloxacin (10.6%), Tmp/Smx (10.6%)		[17]

However, this may become a significant clinical problem as the range of effective antibiotic agents becomes more limited in infections caused by cotrimoxazole resistance [65]. In addition, some studies suggest that TMP/SMX monotherapy may not be the only treatment of choice for infections caused by *S. maltophilia* [66], because monotherapies with any antimicrobials do not achieve adequate clearance of *S. maltophilia*, and even monotherapy is considered inadequate in the management of infections, especially in the case of immunocompromised patients, requiring combination therapy to inhibit or eradicate *S. maltophilia* [67].

The second group of drugs most used in treating infections caused by strains of *S. maltophilia* are fluoroquinolones, mainly levofloxacin [43]. For example, in a study carried out in Mexico, the genetic similarity of strains collected in the same hospital goes from 75 to 100% during seven years, in which they report that the resistance of *S. maltophilia* against TMP/SMX is different in different areas of the world, which is why they recommend the use of levofloxacin as a therapeutic alternative [3], since it shows a susceptibility rate of 81.2%–95.8% [3,38,53,56–58].

Recent studies have reported the resistance of *S. maltophilia* to a variety of antimicrobials (Table 1), including carbapenems, such as imipenem with resistance rates ranging from 45% to 100% and meropenem (92.4%–94%) [24,53,57,61,64]; fluoroquinolones, because active efflux pumps contribute significantly to fluoroquinolone resistance in *S. maltophilia* isolates, such as ciprofloxacin (9.3%–93%) [24,38,53,61,64] and moxifloxacin (1.6%) [24]; ceftazidime (27.1%–100%) [24,53,54,57,61,63,64]; chloramphenicol (14.3%–100%) [24,61,63,64]; cefepime (32.1%–93%) [24,61,64]; aztreonam (84%–>94%) [24,64]; ticarcillin-clavulanic acid [24,53,64]; and minocycline (0.5%–81%) [24,59,64]. The resistance of *S. maltophilia* strains to gentamicin has reached levels of 22%–70% [24,53,61,64], and for the first time, the report of resistance to fosfomycin (34%) and nitrofurantoin (22%) was made [64]. *S. maltophilia* can acquire a high level of resistance to fosfomycin due to mutations in genes encoding metabolic enzymes, allowing it to acquire resistance in laboratory environments [45].

However, other studies have mentioned that drugs with historical favorable susceptibility results include minocycline, with susceptibility rates ranging from 98.9–100% [54,57,62], levofloxacin (81.2%–95.2%) [38,53,56–58], and ceftazidime (28.2%–93.2%) [53,55,58,67], which are the most widely used antibiotics as a last resort for the treatment of *S. maltophilia* infections [57]. In addition, moxifloxacin, colistin (84.4%–100%) [53,55,56], and chloramphenicol have also been used, although they do not appear to be appropriate options for every environment [67]; ticarcillin–clavulanic acid (62.5%) [53] and fluoroquinolones have also been used, even though several authors mention a worrying trend in resistance to these antibiotics. Tetracyclines such as tigecycline (90.5%–100%) [53,56] and doxycycline are also effective drugs and show consistent good activity against *S. maltophilia* in different geographic regions and over different periods. In addition, combination therapies, new drugs, and aerosolized antimicrobials are currently being tested for their ability to treat infections caused by this multiresistant microorganism [7].

Today, it is known that a variety of genes are involved in antibiotic resistance, and it has even been mentioned that *S. maltophilia* can acquire resistance through mutations in resistance genes through horizontal gene transfer. For example, the most reported resistance genes are *Sul1* and class 1 integrases. It has even been reported that there is a significant association between the presence of *Sul1* and class 1 integrons, presenting a gene frequency that can go from 36.4%–100% and 22%–100%, respectively (Table 2), and are considered the main resistance mechanisms to TMP/SMX in *S. maltophilia* [44,53,55,60,64], which has increased resistance to TMP/SMX when associated with transposons, and it is even stated that this gene in *S. maltophilia* isolates could further spread among bacteria through gene transfer. In addition, the *Sul1*, *Sul2*, *intI1*, *dfrA12*, *dfrA17*, and *dfrA27* genes are more prevalent in resistant isolates than in those susceptible to TMP/SMX [60].

Table 2. Presence of resistance and virulence genes in *S. maltophilia* isolates.

Country	Year	Nunber of Isolates	Genes de Resistencia a Antibioticos (%)	Integron Class 1, 2, and 3 (%)	Other Virulence Genes (%)	References
China	2010–2012	426			*gyrA* (100%), *parC* 100%), *smeD* 100%), *smeE* 100%), *smeF* 100%), *smQnr* (25.4%)	[59]
China	2005–2014	300	*Qaceδ1-Sul1* (59.7%), *Sul2* (25.7%)	*Int1* (72.7%)	*Dfra1* (1.3%), *Dfra5* (1.3%), *DfrA12* (11.7%), *DfrA17* (8.3%), *DfrA27* (2.7%)	[60]
Egypt	2013–2015	32	*Sul1* (100%), *Sul2* (8.3%)	*Int 1* (100%)		[53]
Iran	2015–2016	44	*Sul1* (36.4%), *Sul2* (34.1%)	*Int 1* (54.5%)	*SmQnr* (65.9%)	[55]
Mexico	2016–2017	30	*Sul1* (100%), *Qnr* (86.6%), *Sul2* (73.3%)	*Int 1* (80%), *Int 2* (40%), *Int 3* (6.6%)	*Pilu* (96.6%), *Flic* (90%), *Hlyiii* (90%), *Virb* (86.6%), *Plcn1* (83.3%), *RmlA* (83.3%), *Papd* (80%), *Afad* (73.3%), *Hgbb* (66.6%), *Gspd* (53.3%), *Stmpr1* (50%), *Enta* (23.3%), *Mota* (23.3%), Tpsb (20%) All Environmental *S. maltophilia* strains 100% contained the *Virb, Flic, Pilu, Plcni, Qnr,* and *Sul1* genes.	[43]
China	2014	93			*Stmpr1* (79.6%), *Stmpr2* (91.4%), *Smf-1* (94.6%), *Smlt3773* (52.7%)	[62]
Iran	2017–2018	117	*Sul1* (55%), *Sul2* (14.4%)	*Int1* (22%)	*Aadb* (15.2%), *Dfra5* (11.8%),	[63]
Iraq	2016–2020	3569	*Clpa* (93%), *Htpxa* (92%), *Tet A* (92%), *Tet B* (89%), *Blactx-M1* (84%), *Blashv* (71%), *Sul1* (69%), *Dfra* (61%), *Qnr* (55%), *Mcr-1* (24%), *Blaimp1* (23%), *Blaoxa-48* (4%), *Acc (3)-Iv* (6.1%)		*Flic* (93%), *Stmpr1* (87%), *Tpsb* (86%), *Plcn1* (84%), *Virb* (73%), *Fimh* (69%), *RmlA* (69%), *Pilu* (62%), *Hlyiii* (59%), *Gspd* (57%), *Papd* (57%), *Afad* (46%), *Hgbd* (39%), *Mota* (31%), *Enta* (31%)	[64]

The presence of other predominant resistance genes with their respective prevalences, including *Clpa* (93%), *Htpxa* (92%), *Tet A* (92%), *Tet B* (89%), and *Blactx-M1* (84%), has also been identified in *Blashv* (71%), *Dfra* (61%), *Qnr* (55%), *Mcr-1* (24%), *Blaimp1* (23%), *Blaoxa-48* (4%), and *Acc (3)-Iv* (6.1%) [64]. Finally, the Sm*Qnr* quinolone resistance gene has been reported in isolates that are not sensitive to ciprofloxacin, and the prevalence of this gene, like that of *Sul1* in isolates that contain integrons, is a sign of the significant risk of resistance to sulfonamides and fluoroquinolones in clinical isolates of *S. maltophilia* [55].

Antibiotic Resistance Mechanisms

There are molecular mechanisms that contribute to antibiotic resistance. Among the most important are the efflux pumps, the production of β-lactamases, the expression of *Qnr* genes, the presence of class 1 integrons, and the low membrane permeability, among others.

It is known that very complex regulatory mechanisms must be explored to develop a better therapeutic strategy against *S. maltophilia*. For example, a study of genomic and phenotypic analysis of chronic infection in patients with cystic fibrosis mention that *S. maltophilia* populations exhibit constant genotypic and phenotypic heterogeneity and explain that this is due to the "biological cost" that *S. maltophilia* has to pay to successfully adapt to the highly stressful lung environment of patients with cystic fibrosis in the presence of different selection pressures depending on the host environment [54].

There are *S. maltophilia* efflux pumps that belong to the resistance nodulation (RND) cell division family, such as *SmeIJK*, *SmeYZ*, and *SmeOP*, which are composed of an inner membrane protein that binds to the substrate, a protein outer membrane protein (porin), and a membrane fusion protein (MFP), which binds to the inner and outer proteins in the periplasmic space [47]. In addition, ABC, SmrA, and MacABCsm efflux pumps have also been characterized in *S. maltophilia* [68].

The original function of the *SmeDEF* efflux pump in *S. maltophilia* is associated with the ability to colonize plant roots and is triggered by plant-produced flavonoids, and quinolone resistance is a recent function [69].

SmeABC is involved in acquired resistance to β-lactams, aminoglycosides, and quinolones, but does not influence intrinsic resistance [70].

SmeVWX overexpression in clinical isolates of *S. maltophilia* is associated with a high level of resistance to quinolones [71].

The *SmeYZ* pump is a resistance-nodulation-division (RND) efflux pump that is one of the causes of *S. maltophilia* multiresistance and is correlated with virulence-related functions, including motility, flagella formation, biofilms, susceptibility to oxidative stress, and secretion of proteases [72].

SmrA is a member of the ABC multidrug efflux pump family along with MacABCsm; it is a transporter moiety that probably functions as a homodimer and shares structural and functional similarities with each half of the human P-glycoprotein, LmrA, and VcaM. The presence of *SmrA* in *S. maltophilia* may contribute to intrinsic and acquired resistance to this important pathogen [73].

EmrCABsm belongs to the major facilitator superfamily (MFS) and is involved in the extrusion of hydrophobic compounds, including the antibiotics nalidixic acid and erythromycin [74].

As for *SmeJ* and *SmeK* genes, were identified in *S. maltophilia* KM5, a mutant derivative that jointly elevates the MICs of tetracycline, minocycline, and ciprofloxacin confers resistance to levofloxacin [75].

In the case of the MacABCsm pump, it has physiological roles in protecting *S. maltophilia* from oxidative stress and envelope attack and in biofilm formation, which may be the reason why it can be expressed constitutively in the absence of antibiotics, and it is highly conserved in *S. maltophilia* isolates, presenting intrinsic resistance to macrolides, aminoglycosides, and polymyxins [68].

The SmeOP-TolCSm efflux pump is the fusion of the *SmeO* and *SmeP* operons with the *S. maltophilia* TolC porin (TolCSm), forming the assembly of a pump of the RND family

involved in the extrusion of antibiotics such as nalidixic acid, amikacin, doxycycline, gentamicin, erythromycin, and other non-antibiotic compounds, such as sodium dodecyl sulfate, crystal violet, carbonyl cyanide 3-chlorophenylhydrazone, and tetrachloro salicyl anilide [76].

On the other hand, the production of β-lactamases is the leading cause of the difficulties in treating infections caused by *S. maltophilia*, as is already known, due to the intrinsic and acquired resistance of these strains to a wide range of antibiotics and chemotherapeutic agents. All strains produce β-lactamases L1 and L2, which confer intrinsic resistance to β-lactam antibiotics [47].

The low permeability of the membrane is a mechanism exhibited by *S. maltophilia* due to the presence of both the cell membrane and the peptidoglycan wall, making the outer membrane an effective barrier, but the mutated strains are permeable. Altered outer membrane or other lipopolysaccharide structures exhibit modified sensitivity to antibiotics [47].

5. Alternative Treatments

Investigations are currently underway regarding the use of specific bacteria to treat infections with the potential to circumvent or delay the development of antimicrobial resistance [77]. In combination with several other proven approaches, phage therapy, epigallocatechin-3-gallate (EGCG), essential oils, nanoemulsions, and the use of cationic compounds are known as promising alternatives that could be incorporated into the control arsenal of *S. maltophilia* [78].

Bacteriophages (phages) are the most abundant entities on earth, with ten times more phages than the estimated number of bacteria in the biosphere [79]. They are viruses that recognize and bind to a specific host bacterium by recognizing a cell surface receptor to infect and kill the target bacterial species [33].

An example of this is the isolation and characterization of at least 20 *S. maltophilia*-specific phages, of which 11 stand out for their therapeutic potential: Sm1, IME13, IME15, S3, Sm14, ΦSMA5, DLP1, DLP2, DLP4, DLP5, and DLP6 [80]. It is estimated that around 15 temperate phages of *S. maltophilia* that have been characterized carry genes that encode virulence factors or proteins involved in antibiotic resistance with the capacity to cause lysogenic conversion in *S. maltophilia* [81]. There are currently 57 described phage genomes for *S. maltophilia* and 6 phages characterized, but complete genomic sequences are lacking, suggesting that understanding *S. maltophilia* phage diversity is just beginning [82].

The AXL1 bacteriophage, belonging to the family Siphoviridae of the B2 morphotype isolated from soil, is the sixth *S. maltophilia* phage that has been identified that can bind to the type IV pili as a cell surface receptor for infection, interacting directly with the subunit of pilin PilA1 and requiring a functional pilus capable of retraction for successful infection [82]. In addition, the same investigators characterized a new phage that is active against the multidrug-resistant bacterial pathogen *S. maltophilia*, of the Siphoviridae family, which they named AXL3, with a genome of 47 545 bp and that uses type IV pili as a host receptor, which interact directly with the PilA subunit for host recognition based on host-cell retraction of the type IV pili to reach the cell surface and produce successful infection [83].

Another characterized *S. maltophilia* phage is ΦSHP3, also from the Siphoviridae family; it is the only transposable phage isolated from *S. maltophilia* to date that is like B3 and has a genome of 37.6 kb. In addition, it encodes an RdgC exonuclease involved in phage recombination [79].

Transcriptomic studies have also been carried out to collect data on the response mechanisms of *S. maltophilia* to fosfomycin and to determine if the changes caused by fosfomycin are related to intermediate metabolites of this pathway, such as phosphoenolpyruvate PEP (its structural homolog) and glyceraldehyde-3-phosphate (an intermediate metabolite of the mutated pathway in fosfomycin-resistant mutants), whose inactivation leads to fosfomycin resistance in *S. maltophilia*. These compounds reduce the expression of genes related to

transport across the membrane, such as the *smeZ* efflux pump gene and the fructose phosphotransferase system. Inhibition of *smeYZ* efflux pump expression, which confers intrinsic resistance to aminoglycosides, suggests that fosfomycin, PEP, or GA-3P could be used in combination with *smeYZ* substrates, reducing their expression and increasing susceptibility to these antibiotics. However, more studies are needed to determine the best inhibitor, which could be used in clinics for the treatment of infections caused by *S. maltophilia*, for which the combined therapies of TMP/SMX and fosfomycin could exhibit more significant activity since they regulate the upregulates genes for amino acid biosynthesis, motility, chemotaxis, and stress response. However, there were no transcriptional changes in genes related to cell wall biosynthesis, such as *murA*, which is the biosynthetic pathway inhibited by fosfomycin. There were also no changes in genes related to the lower Embden–Meyerhof–Parnas metabolic pathway, which includes PEP and GA-3P as intermediate metabolites and is involved in fosfomycin resistance. On the other hand, they induce the expression of *msrA* methionine sulfoxide reductases (defense proteins against oxidative stress) in *S. maltophilia*. No significant differences were observed in the expression of any of the genes involved in peptidoglycan synthesis; therefore, the adaptation of *S. maltophilia* to the presence of fosfomycin does not require changes in the activity of the classical determinants involved in the activity and resistance to this antibiotic. Therefore, the importance of the previous work lies in describing the efflux pump inhibitors that can be used as antibiotic adjuvants to counteract antibiotic resistance in *S. maltophilia* [45].

Another alternative that we can mention is a plant-derived compound, emodin, which is a naturally occurring anthraquinone found in the roots and barks of numerous plants, molds, and lichens, and emodin has been shown to inhibit biofilm formation at 20 μM in *Stenotrophomonas maltophilia* significantly. Furthermore, cells that were incubated with emodin detached and dispersed from the surface, and it is likely that emodin penetrates the biofilm and interferes with the quorum sensing (QS) system, which might be suitable to become an antiviral and antibacterial agent [84].

6. Antibiotics and Biofilm Formation

Among the multiple mechanisms involved in resistance to antibiotics, the formation of biofilms is one of them, and this characteristic has set the tone for seeking new treatment alternatives and being able to deal with infections [77].

Since the formation of biofilms seems to play a crucial role in the pathophysiology of infections due to *S. maltophilia* [24], the average capacity for biofilm formation by biofilms has been studied by various authors of *S. maltophilia*, classifying them as follows (Table 2): strong production of biofilms with a prevalence ranging from 10% to 98.4% [24,38,43,57,62,64], moderate biofilm production with a prevalence of 21.3%–46.6% [24,44,57,64], and weak biofilm producers with a prevalence of 16%–36.6% [24,43,57,64].

Therefore, these data allow us to glimpse the potential for biofilm formation by drug-resistant strains [64] and demonstrated that there are genes of *S. maltophilia* involved in the formation of biofilms that seem to be related to resistance to antibiotics, as stated by [24], mentioning that more than 58% of the isolates that showed resistance to ticarcillin/acid clavulanate, ciprofloxacin, ceftazidime, and doxycycline are consistent with the development of strong biofilms. Therefore, statistical analysis shows an association between biofilm-forming ability and antibiotic resistance pattern among all clinical isolates, indicating that resistance to ticarcillin/clavulanic acid, ciprofloxacin, ceftazidime, and doxycycline among strong biofilm producers was significantly higher than that of moderate, weak, and non-biofilm producers. This type of biofilm production was related to the presence of the *smf-1*, *rmlA*, *spgM*, and *rpfF* genes associated with biofilm formation capacity; the participation of the *rpfF* gene was detected in all biofilm producers (strong, moderate, and weak), while the presence of *spgM* was confirmed in all strong, all weak, and some moderate biofilm producers, and in the case of the *rmlA* gene, its presence was confirmed in all moderate biofilm producers weak and in some strong producers [24]. Some other works mentioned the frequency percentages of these genes that are highly

conserved among clinical strains isolated from *S. maltophilia* related to biofilm production, ranging from *rmlA* 82.8%-98.0%, *spgM* 92.5%-100%, and *rpfF* 64.5%-84.7% (Table 3). Regarding its function, *rmlA* is involved in the biosynthesis of nucleotide sugar precursors of lipopolysaccharide (LPS) and exopolysaccharides (EPS) [74], *spgM* is involved in lipopolysaccharide biosynthesis and encodes a bifunctional enzyme with phosphoglucomutase activities and phosphomannomutase [85], and *rpfF* participates in the synthesis of DSF (cis -11-methyl-2-dodecenoic acid) synthase [86].

Table 3. Ability to form biofilms with *S. maltophilia* and associated genes.

Country	Year	Nunber of Isolates	Biofilm Genes (%)	Biofilms (%)	References
Argentina	2004–2012	63		Strong biofilm (98.4%)	[38]
Iran	2016–2017	150	*RmlA* (98.0%), *SpgM* (97.3%), *RpfF* (70.0%)	Strong Biofilm (46.0%), Moderate Biofilm (21.3%) Weak Biofilm (31.3%), No Biofilm (1.3%)	[24]
Mexico	2016–2017	30	*RmlA* (83.3%)	Strong Biofilm (10%), Moderate Biofilm (46.6%), Weak Biofilm (36.6%), No Biofilm (6.66%)	[43]
China	2014	93	*RmlA* (82.8%), *SpgM* (92.5%), *RpfF* (64.5%)	Strong Biofilm	[62]
Iran	2018–2019	85	*RpfF* (89.4%), *SpgM* (100%), *RmlA* (84.7%)	Strong Biofilm (34.1%), Moderate Biofilm (37.6%), Weak Biofilm (28.2%)	[57]
Iraq	2016–2020	3569	*RmlA* (69%)	Strong Biofilm (51%), Moderate Biofilm (33%), Weak Biofilm (16%)	[64]

Other studies show that the production of strong biofilms by clinical isolates of *S. maltophilia* is significantly associated with the existence of *fliC*, *plcNi*, *fimH*, *pilU*, and *papD* genes [64].

7. Public Health Problem

S. maltophilia is recognized as an important nosocomial pathogen that can cause serious infections, including bacteremia [51], sepsis, pneumonia, meningitis after neurosurgical procedures, endocarditis, necrotizing otitis, skin infections including soft tissue infection, keratitis, acute respiratory tract infection, urinary tract infection, septic arthritis, and endophthalmitis in immunocompromised patients, among others. Additionally, it can increase the risk of infection due to factors associated with prolonged hospitalization in intensive care units because of HIV, cancer, cystic fibrosis, neutropenia, surgical wounds, artificial respiration, and the previous administration of broad-spectrum antibiotics [78].

Respiratory tract infections. Due to the biofilm-forming properties, *S. maltophilia* often colonizes the respiratory tract of hospitalized patients; the main causes of mortality among these patients are acute respiratory distress syndrome (ARDS) and septic shock, and one of the main predisposing factors that prevailed was mechanical ventilation [87].

Cancer. *S. maltophilia* infections cause concern in patients with cancer and blood disorders because they have increased in recent years. *S. maltophilia* has been isolated from cases of hematologic malignancy acute myeloid leukemia, lymphomas, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, severe aplastic anemia, solid cancer, and in hematopoietic stem cell transplant recipients. Among the factors that

influence mortality in cancer patients due to *S. maltophilia* infections are severe sepsis and the duration of antibiotic therapy [88].

Bloodstream infections caused by *S. maltophilia*, mainly in immunocompetent patients. Nosocomial bacteremia is defined as the detection of *S. maltophilia* in blood samples obtained at least 48 h after admission for clinical symptoms, are associated with a considerably high mortality rate in patients with cardiac conditions, and were strongly associated with independent mortality in patients with hypoalbuminemia. At the same time, catheter replacement plays an important role in patient survival at 30 days [89].

Ocular infections. *S. maltophilia* ocular infections are opportunistic infections followed by the instability of the ocular surface. *S. maltophilia* is a relatively uncommon pathogen of keratitis, and *S. maltophilia* keratitis is associated with several risk factors for ocular surface instability. Mixed use of fluoroquinolones, beta-lactams, and aminoglycosides should be considered as the treatment of choice, and in cases of polymicrobial infections, clinical attention is required due to antibiotic resistance and poor outcomes [90].

Liver abscess. This is a condition of suppurative infection of the liver parenchyma of bacterial cause, and although the formation of a liver abscess due to infection by *S. maltophilia* in immunocompetent patients is usually a very rare clinical manifestation, treatment with parenteral levofloxacin and oral trimethoprim–sulfamethoxazole along with pigtail catheter drainage and other appropriate supportive therapies led to resolution of the abscess [91].

Meningitis. *S. maltophilia* is a rare but important cause of nosocomial meningitis, associated with previous hospitalizations, neurosurgical interventions, exposure to antibiotics, and chronic diseases such as diabetes and malignant tumors. Its optimal management is not yet well-defined, so the management of *S. maltophilia* meningitis is a therapeutic challenge due to its high resistance to multiple antibiotics. However, the combination based on trimethoprim and sulfamethoxazole has been shown to be successful [91].

Spinal cord. Stenotrophomonas maltophilia has been isolated from spinal cord aspirates after more than a month of unsuccessful empirical treatment with six different antibiotics. However, treatment with sulfamethoxazole–trimethoprim and minocycline has been successful. As a risk factor, it has been mentioned that cupping therapy is an alternative medicine that should be recognized as a possible risk of severe infections in the spinal cord [92].

Skin. *S. maltophilia* can cause skin and soft tissue infections with variable presentations, including metastatic cellulitis, primary cellulitis, and ecthyma gangrenosum. Associated risk factors are hematologic malignancies and chemotherapy, neutropenia, the presence of a central venous catheter, and exposure to broad-spectrum antibiotics. They lead to high mortality and require specific treatment due to high resistance to antimicrobials [4,93].

Infections associated with hospital medical care (nosocomial) are the most common complications that affect hospitalized patients, which is why they have become one of the largest and most important public health problems worldwide, primarily in developing countries, due to increased associated morbidity and mortality rates [94]. That is why *S. maltophilia* has come to be considered an etiological agent of various infectious diseases [3].

It has been reported that in patients with bacteremia, crude mortality rates range from 34.4% to 65% [51,95], and in a study conducted in the United States over 12 years (1993–2004) in which some hospitals participated in determining antimicrobial susceptibility profiles of Gram-negative bacilli with intensive care unit patients, *S. maltophilia* was reported among the 11 most frequently isolated microorganisms, occupying eighth place, with 4.3% of a total of 74,394 isolates [96].

In recent years, the prevalence and incidence of *S. maltophilia* have increased significantly in patients with cystic fibrosis, who have a higher risk of *S. maltophilia* infections than the general population. In addition, in low-income countries, the prevalence of *S. maltophilia* was significantly lower. However, in high-income countries, the incidence was higher. In

the case of age, the prevalence of *S. maltophilia* increased in all age strata and in young adults in middle- and high-income countries [97].

Although chronic *S. maltophilia* infections are associated with a nearly three-fold increased risk of death or lung transplantation in patients with cystic fibrosis, it remains unclear whether *S. maltophilia* infection is just a marker of the severity of cystic fibrosis lung disease or if it leads to an acceleration of disease progression [98,99].

In the case of patients hospitalized for COVID-19, recent studies report the development of secondary bacterial infections in affected patients. One of the most frequently isolated bacteria was *S. maltophilia*, occupying even the second place in terms of isolated bacteria, exhibiting multiple drug-resistance phenotypes, and limiting the prescription of empirical antibiotics, and, therefore, these patients are associated with higher mortality and prolonged hospitalization [100].

Additionally, secondary infection by *S. maltophilia* in patients with SARS-CoV-2 pneumonia has become a health problem due to the use of intravenous corticosteroids, excessive treatment with empirical antibiotics, and poor hygiene practices in patients, with invasive mechanical ventilation that facilitated colonization and infection by *S. maltophilia* and, therefore, increased hospital stays and mortality of patients with COVID-19 [101].

Likewise, there is an increased risk of bloodstream infections among critically ill patients due to COVID-19, and the pathogens detected in the bloodstream include *S. maltophilia* [102,103], being the most common cause of coinfection in addition to being related to intubations and mechanical ventilation, and in some studies, they were only sensitive to cotrimoxazole [104].

Another crucial factor to consider is the relationship between environmental and clinical strains since it is important to study the molecular epidemiology of clinical and environmental strains of *S. maltophilia*, allowing to demonstrate which ones have greater virulence capacity, antibiotic resistance, biofilm formation capacity, and adherence profiles, since it is known that these characteristics can promote the spread and persistence of *S. maltophilia*, becoming a significant health problem due to the exchange of resistance and virulence genes between environmental and clinical strains.

8. Conclusions

The processes involved in forming biofilms in *S. maltophilia* and the virulence factors associated with *S. maltophilia* should be further studied since there need to be consistent guidelines for the effective treatment of biofilm-related *S. maltophilia* infections. However, the relationship of biofilm-associated genes and new treatment options could envision a new path to eradicate *S. maltophilia* as alternatives to conventional antibiotics, which lead to greater multiresistance and less efficacy every day.

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