Biomolecules & Biomedicine

REVIEW

Stenotrophomonas maltophilia infections – Biofilm-mediated virulence, multidrug resistance, clinical impact, and emerging treatment strategies: A review

Noha A. Juma[1], Noura Daffa[1], Mona Alqarni[1], Bandar Hasan Saleh[1,2], Abdelbagi Alfadil[1], Tariq Ekhmimi[1], Jawahir A. Mokhtar[1,2,3], Dalya Attallah[2], Khalil Alkuwaity[3,4], Sarah Almuhayya[5], Salem Agabawi[6], Turki Asiri[7], Ziyad Omar Allehebi[7], Mohammad Hassan Albar[8,9], Khalid Ahmed[10], Ibrahim Abu[11], Turki M. Alharthi[12], Ahmed Gassim Bukhari[4], and Karem Ibrahem[1,2*]

Stenotrophomonas maltophilia **is an opportunistic, multidrug-resistant (MDR), Gram-negative bacterium that has emerged as an important cause of hospital- and community-acquired infections, particularly in immunocompromised, critically ill, and hospitalized patients. Its increasing clinical relevance is driven by extensive virulence determinants, biofilm formation, intrinsic and acquired antimicrobial resistance, and persistence within healthcare-associated environmental reservoirs. This narrative review summarizes current evidence on the epidemiology, pathogenic mechanisms, antimicrobial resistance, and therapeutic management of *S. maltophilia*, with a particular focus on emerging treatment strategies. A literature search of PubMed, Scopus, Web of Science, and Google Scholar was performed to identify relevant studies published between 1997 and 2026. The available evidence demonstrates that biofilm formation, quorum sensing, adhesion factors, secretion of extracellular enzymes, and multiple resistance mechanisms—including β-lactamases, multidrug efflux pumps, and horizontally acquired resistance genes—substantially contribute to persistent infections and therapeutic failure. Hospital outbreaks are frequently associated with contaminated water systems, sinks, and medical devices, emphasizing the importance of environmental surveillance and infection control. Trimethoprim-sulfamethoxazole (TMP-SMX) remains the recommended first-line therapy, whereas minocycline, tigecycline, fluoroquinolones, and cefiderocol represent important alternatives for selected patients. Emerging approaches, including novel tetracyclines, bacteriophages, bacteriocins, ceragenins, anti-biofilm agents, and plant-derived compounds, have demonstrated promising preclinical activity against MDR and biofilm-associated infections, although robust clinical evidence remains limited. Continued surveillance, antimicrobial stewardship, pharmacokinetic/pharmacodynamic-guided therapy, and well-designed prospective clinical studies are essential to optimize the management of *S. maltophilia* infections and facilitate the translation of emerging therapeutic strategies into clinical practice.**

Keywords: *Stenotrophomonas maltophilia*, multidrug resistance, biofilm, virulence, novel therapy, phage therapy.

Introduction

Stenotrophomonas maltophilia is an opportunistic, multidrug-resistant, Gram-negative bacterium primarily responsible for infections in immunocompromised or hospitalized patients. Its pathogenicity is driven by various virulence factors, biofilm formation, and intrinsic resistance mechanisms [1]. As an ubiquitous environmental organism, *S. maltophilia* is widely distributed in soil and water, frequently associating with plants and animals [2]. Globally, *S. maltophilia* is increasingly recognized as a significant cause of respiratory infections in humans. Beyond pulmonary diseases, it can induce a range of severe infections and is an emerging agent in healthcare-associated infections [3]. Among non-fermenting Gram-negative bacteria, it ranks as the fourth most frequently isolated organism from positive blood cultures, following *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and the *Burkholderia cepacia* complex [3, 4]. The bacterium exhibits intrinsic resistance to numerous antibiotics due to the presence of

[1]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Department of Clinical Microbiology Laboratory, King Abdulaziz University Hospital, Jeddah, Saudi Arabia; [3]EcoHealth Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [4]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia; [5]Department of Clinical Laboratory Science, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia; [6]Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [7]Department of Microbiology and Parasitology, Faculty of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia; [8]Department of Obstetrics and Gynecology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [9]King Abdulaziz University Hospital, Jeddah, Saudi Arabia; [10]Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [11]Department of Preventive Medicine and Public Health, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [12]Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia.

*Correspondence to Karem Ibrahem: kaibrahem@kau.edu.sa

DOI: 10.17305/bb.2026.14293

© 2026 Juma et al. This article is available under a Creative Commons License (Attribution 4.0 International, as described at https://creativecommons.org/licenses/by/4.0/).

multiple antimicrobial resistance genes [5]. Continuous monitoring of *S. maltophilia* is crucial given the rising incidence of community-acquired infections and its pervasive presence in clinical environments [6].

This review synthesizes current understanding of the major virulence determinants of *S. maltophilia*, its global epidemiology, resistance mechanisms, and clinical impact as an emerging multidrug-resistant pathogen. Special emphasis is placed on integrating recent advancements in understanding its pathogenicity, evolving antimicrobial resistance profiles, diagnostic challenges, and current therapeutic approaches. Furthermore, this review identifies existing knowledge gaps and discusses emerging and alternative treatment strategies that could enhance future management of *S. maltophilia* infections, particularly in healthcare settings.

Methodology

This narrative review was conducted based on a comprehensive literature search for published research on *S. maltophilia*. PubMed, Scopus, Web of Science, and Google Scholar databases were systematically searched for relevant articles published between 1997 and 2026. This timeframe was selected to encompass foundational studies describing antimicrobial resistance and clinical features of *S. maltophilia*, through to the most recent literature addressing molecular epidemiology, virulence mechanisms, emerging resistance trends, and novel therapeutic strategies. Additionally, older seminal publications were included when deemed essential for contextualizing and developing the topic.

Combinations of keywords and Medical Subject Headings (MeSH) were employed, including "Stenotrophomonas maltophilia," "virulence factors," "multidrug resistance," "antimicrobial resistance," "epidemiology," "biofilm," "pathogenesis," "diagnosis," "treatment," and "alternative therapy." Original research articles, clinical studies, surveillance reports, and relevant reviews were considered for inclusion. Article selection was based on relevance to the review's scope and their contribution to clarifying the emerging clinical significance and challenges associated with *S. maltophilia* infections.

Epidemiology

S. Maltophilia is a prominent healthcare-associated pathogen, with increasing prevalence among immunocompromised individuals and patients in intensive care units (ICUs) [3, 7]. It is linked to severe infections and elevated mortality rates, which vary depending on patient-specific factors, environmental healthcare exposure, and whether the organism represents a true infection or mere colonization [8]. Prompt identification of high-risk patients, 強化 infection control measures, and appropriate antimicrobial therapy are critical for improving outcomes [9]. This organism is widely distributed in hospital environments, where it can act as either a true pathogen or a colonizer. As a colonizer or environmental contaminant, it can be isolated from hospital objects such as catheters, ventilator circuits, endoscopes, and water systems [10, 11]. Furthermore, it forms biofilms on moist surfaces, including dental unit waterlines and respiratory equipment, thereby facilitating colonization and infection [12].

The rising incidence of *S. maltophilia* infections is driven by the widespread use of broad-spectrum antibiotics and invasive medical devices in various healthcare settings [13]. A global meta-analysis of 95 studies (from 6,770 records) reported an overall prevalence of 5.3%, with the highest rates in the Western Pacific (10.5%) and the lowest in the Americas (4.3%). Resistance rates were highest for cefuroxime (99.1%) and lowest for minocycline (4.8%). Resistance trends have escalated over time, particularly for tigecycline and ticarcillin-clavulanic acid. Trimethoprim-sulfamethoxazole (TMP-SMX) remains the most effective treatment option [14].

Notably, a 19-year study identified 4,466 *S. maltophilia* infections, predominantly in adult and surgical ICUs (32.2%), followed by cardiology (29.8%) and pediatric ICUs (10%). Its prevalence increased from 7% (2004–2007) to 15% (2020–2022). Resistance was highest to ceftazidime (72.5%), followed by levofloxacin (56%) and TMP-SMX (14.05%). A significant increase occurred during the COVID-19 pandemic ($P = 0.0017$), with projections suggesting a prevalence rate of 15.08% by 2030. These findings underscore the necessity for continuous surveillance, infection control, and antimicrobial stewardship [15].

Moreover, an analysis of 93 isolates from a Chinese teaching hospital revealed that most samples originated from male patients (62/93) and sputum (81/93). Genetic typing identified 61 sequence types (45 novel), indicating no dominant clones and weak genetic relatedness. Resistance rates were low for TMP-SMX (9.7%) and levofloxacin (4.3%), and all isolates were susceptible to minocycline. High positivity was observed for virulence (up to 94.6%) and biofilm genes (up to 92.5%), with strong biofilm formation (mean $OD_{492} = 0.54$). ICU infections were associated with immunosuppression and antibiotic overuse. Overall, *S. maltophilia* demonstrated high virulence but limited resistance, emphasizing the need for prudent antibiotic use and robust infection control. A proportion of isolates represented colonization rather than true infection, particularly in respiratory samples, and infected patients experienced worse outcomes than colonized patients [16].

Data from 1,412 Chinese hospitals (2014–2021) were analyzed to assess prevalence and resistance trends. Among 514,768 isolates, the overall prevalence remained stable at approximately 2.1%, with higher rates in ICUs and elderly patients. Resistance to TMP-SMX decreased from 9.8% to 7.5%; levofloxacin resistance slightly increased from 8.5% to 9.5%, and minocycline resistance remained low (~2%). Despite its generally low resistance, high rates in blood isolates suggest minocycline remains the most effective option. Ongoing surveillance, strict infection control, and further research into emerging treatments such as cefiderocol are crucial [8].

Significantly, *S. maltophilia* has been identified in both hospital and community settings, particularly in immunocompromised patients. Major risk factors include malignancy, cystic fibrosis, immunosuppressive therapy, indwelling catheters, and prior broad-spectrum antibiotic use. Its global

Table 1. Summary of key outcomes, prevalence, patient outcomes, and outbreak investigations of *S. maltophilia* in hospital and community settings

Aspect	Key findings	References
Reservoirs and sources	Hospital water systems and devices (catheters, ventilators, humidifiers, endoscopes, faucets, drains, dialysis water); also dental units and contact lens solutions.	[7–9]
Prevalence and incidence	Global prevalence ~5.3%; highest in Western Pacific (10.5%). ICU cases mainly adult/surgical (32.2%) and cardiology (29.8%). Increasing trend: 7% (2004–2007) → 15% (2020–2022).	[10–12]
Patient outcomes	30-day mortality ~28%; higher in critically ill patients (~32.8%). Risk factors: septic shock, comorbidities, prior antibiotics. Early therapy improves outcomes.	[16], [18]
Outbreak reports	ICU outbreaks linked to contaminated faucets/water systems. México: 21 clinical + 9 environmental isolates. Pediatric ICU: 12 patients, multiple genotypes, faucet source confirmed.	[20], [21]

Abbreviation: ICU, intensive care unit.

prevalence has risen from 0.8%–1.4% (1997–2003) to 1.3%–1.68% (2007–2012). Resistance to ceftazidime, ticarcillin-clavulanate, and fluoroquinolones has increased. Tetracyclines, especially minocycline, tigecycline, and doxycycline, continue to show strong efficacy, and novel agents and combination therapies are under investigation to combat this multidrug-resistant pathogen [17].

A retrospective study analyzed 39 cases of *S. maltophilia* bacteremia at the Sanjay Gandhi Postgraduate Institute, Lucknow (July 2021–July 2022), to identify risk factors and outcomes. The mean age of patients was 46 years (69% men). Indwelling catheters (53.8%) and pulmonary infections (46.2%) were the most common risk factors. Isolates showed high susceptibility to minocycline (94.9%), ticarcillin-clavulanic acid (87.2%), levofloxacin (84.6%), and TMP-SMX (84.6%). The 30-day mortality rate was 28.2%. Early targeted therapy and strict infection control can reduce mortality and length of hospital stay in patients with *S. maltophilia* bacteremia [18].

A systematic review and meta-analysis, utilizing eight major databases, identified the highest risks associated with long hospital stays (OR = 14.56), mechanical ventilation (OR = 14.16), use of >3 antibiotics (OR = 6.21), endotracheal intubation (OR = 6.07), and tracheotomy (OR = 3.77). A separate retrospective study on adult patients with *S. maltophilia* isolated between 2020 and 2024 involved 97 patients; 62.9% had infections, and 37.1% were colonized. Infected patients often presented with cardiovascular diseases and immunosuppression. Targeted therapy, primarily TMP-SMX, was administered to most patients. Mortality was significantly higher in infected patients (32.8%), particularly those with septic shock, cardiovascular disease, or prior antibiotic use. Lack of appropriate therapy, cardiovascular disease, and septic shock were independent predictors of 30-day mortality [19, 20].

Recently, an outbreak of *S. maltophilia* occurred at the Children's Hospital of México Federico Gómez. Thirty isolates (21 clinical and 9 environmental) from pediatric patients and hospital faucets were analyzed. Molecular typing revealed seven pulsotypes, with three (P2, P3, and P7) shared between clinical and environmental strains, indicating cross-contamination. High resistance rates were observed for tetracycline (80%) and TMP-SMX (76.6%), with prevalent resistance genes (sulfonamide-resistant dihydropteroate synthase 1 gene [*sul1*], quinolone resistance gene family [*qnr*], class 1 integron integrase gene [*intI1*]) and virulence genes (type IV pilus retraction ATPase gene [*pilU*], hemolysin III family protein gene [*hlyIII*], glucose-1-phosphate thymidylyltransferase gene [*rmlA*]). Several isolates exhibited motility, adherence, and moderate biofilm formation. Monthly faucet disinfection effectively controlled the outbreak, highlighting the importance of environmental hygiene in preventing *S. maltophilia* transmission [21].

In another recent incident, 12 pediatric ICU patients developed *S. maltophilia*-associated bloodstream infections. Of 120 samples, 31 (26%) tested positive for *S. maltophilia*. Pulsed-field gel electrophoresis (PFGE) revealed 10 genotypes grouped into three clusters, with the largest genotype (genotype 1) comprising 19 isolates from both patients and a pull-out faucet in the pediatric intensive care unit (PICU), identified as the outbreak source. Pull-out faucets facilitate biofilm formation and persistence. Regular monitoring of hospital water sources is essential, and faucet design should be a consideration during infection control and outbreak investigations [22] (Table 1).

An outbreak of *S. maltophilia* was investigated, linked to contaminated ready-to-use syringes containing liquid lithium and heparin used for arterial blood gas collection at a university hospital. Following a surge in *S. maltophilia* blood cultures (September–November 2021), an outbreak investigation and case-control study (52 cases and 56 controls) were conducted. Potential sources were cultured, and isolates were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and analyzed for genetic relatedness using PFGE. Significant risk factors, including central venous catheter use, surgery, and arterial blood gas collection, were identified. *S. maltophilia* was detected in commercial syringes, and PFGE confirmed the genetic identity between clinical and syringe isolates. The outbreak was traced to improper sterilization of heparinized preparations and resolved after discontinuing the affected syringes. Contaminated disposable medical equipment can also be a source of infection. Sterilization methods for liquid-filled injectors should be re-evaluated, and close collaboration between infection control teams and microbiology laboratories is essential [23].

An ICU outbreak of *S. maltophilia*, linked to environmental contamination, identified sink drains as the likely source. *S. maltophilia* was isolated from all sink drain samples (5/5),

whereas detection rates were lower in splash zones (10%), air samples (20%), and bed rails (20%). Medical supplies were frequently located within sink splash zones. After installing sink drain covers in the affected rooms, repeat cultures showed no *S. maltophilia* growth except in air samples. Sink drains serve as key reservoirs and likely sources of *S. maltophilia* transmission in the ICU. Environmental modifications, such as installing drain covers, effectively reduce contamination and help control outbreaks [24]. An ICU outbreak of *S. maltophilia* was investigated to identify risks from contaminated drinking water devices. Between 2009 and 2011, isolates from 23 patients belonged to two dominant genotypes, distinct from other sporadic strains. Most samples (74%) were from respiratory sources, and infections were acquired in the ICU. Environmental testing detected outbreak strains in two sinks and in the ICU kitchen drinking water cooler, where *S. maltophilia* formed biofilms inside the tubing. After the contaminated cooler was removed, the monthly incidence decreased to $< 2\%$. Contaminated water devices can serve as persistent reservoirs for *S. maltophilia* in ICUs, emphasizing the need for strict monitoring and maintenance of hospital water systems [25].

S. maltophilia accounts for approximately 2% of ICU-acquired pneumonia cases and ranks among the top 10 pathogens in EU/EEA hospitals. An *S. maltophilia* outbreak in an ICU in northern Italy involved epidemiological analysis, environmental testing, and strain comparison using multilocus sequence typing. Among the seven clinical isolates, six were susceptible to TMP-SMX, and one showed resistance. Six patient isolates and one environmental isolate (from a trolley) shared the same sequence type (ST4), indicating cross-transmission during patient care. Control measures have been implemented to prevent further spread [7]. *S. maltophilia* caused 13 bloodstream infections in ICU patients at a California hospital between April 2022 and September 2023. A matched case-control study identified exposure to iodinated contrast medium (Omnipaque-300), propofol, and fentanyl as significant risk factors. The investigation revealed deficiencies in the cleaning and storage of medical equipment and patient care supplies, although the outbreak strain was not recovered from the environment. Transmission occurred through improper infection control practices, highlighting the need for proper equipment disinfection and safe medication handling to prevent contamination [26].

Pathogenesis

Infections caused by multidrug-resistant Gram-negative bacteria such as *S. maltophilia* are increasing worldwide. It has become more significant during the COVID-19 pandemic as a frequent respiratory co-infecting pathogen [27].

S. maltophilia pathogenesis is multifactorial, involving adhesion, enzyme secretion, biofilm formation, quorum sensing, and high levels of antibiotic resistance [28]. These features enable it to cause severe and persistent infections, particularly in immunocompromised and hospitalized patients, making it a challenging pathogen to control and treat [28].

S. maltophilia employs surface components, including lipopolysaccharides, pili/fimbriae, and flagella, to attach to host tissues and medical devices, thereby enabling colonization and subsequent infection [1, 4]. Moreover, *S. maltophilia* is responsible for diverse infections, including severe lung diseases in patients with cystic fibrosis. Its high antibiotic resistance and multiple virulence factors, such as lytic enzymes, serine proteases, and strong biofilm-forming ability, contribute to both acute and chronic infections. Although the key genes involved in colonization and biofilm development have been identified, the underlying mechanisms remain unclear. It secretes a range of enzymes (proteases, lipases, deoxyribonucleases (DNases), hemolysins, and gelatinases) that degrade host tissues, evade immune responses, and promote invasion [29]. *S. maltophilia* readily develops strong biofilms on medical devices and host tissues, shielding it from antibiotics and the immune system. Biofilm capability plays a key role in persistent device-related infections [30]. Many virulence factors, such as enzyme secretion and biofilm development, are controlled by quorum sensing, which enables bacteria to coordinate gene expression according to population density [29]. Bacterial survival and virulence are supported by efficient iron uptake systems and flexible metabolism, including the ability to catabolize amino acids, allowing for adaptation to different environmental conditions [31, 32]. Although generally considered to have low virulence, *S. maltophilia* can cause severe infections and plays a key role in polymicrobial infections. During the COVID-19 pandemic, it has emerged as a common cause of respiratory coinfections and bacteremia in critically ill patients. Its adaptability to hostile environments and flexible metabolic pathways contribute to its virulence [28].

Deleting the 2,3-bisphosphoglycerate-dependent phosphoglycerate mutase gene (*gpmA*) gene, which encodes phosphoglycerate mutase, reduces early biofilm formation on both biotic and abiotic surfaces. This finding suggests a link between metabolism and biofilm development. The effects of different carbon sources on growth and biofilm formation were also examined. The wild-type strain grew better on amino acids than on glucose, under both planktonic and biofilm conditions, whereas the *gpmA* mutant showed impaired growth on amino acids. The addition of glucose or ribose restored the growth of the mutant. These findings indicate that *S. maltophilia* likely channels amino acid carbon through gluconeogenesis into a metabolic pathway essential for planktonic and biofilm growth, suggesting potential metabolic targets for future therapeutic strategies [30]. The role of chaperone/usher pili in biofilm formation was also investigated. Deletion of the major pilin gene of the SMF-1 chaperone/usher pilus (*smf-1*) resulted in reduced biofilm formation compared to the wild type, confirming its role in attachment. A second pilus cluster, CBL chaperone/usher pilus gene cluster (cbl), has also been identified, whose mutation impairs biofilm development. Electron microscopy suggested that the loss of one pilus was not compensated for by the loss of another. Moreover, infection studies in *Galleria mellonella in vivo* model have shown increased virulence in smf-1 single and smf-1 cbl double mutants. These findings highlight how distinct pili contribute to the transition between acute and chronic infection states and may serve as potential therapeutic targets [33] (Table 2).

Table 2. Clinical risk factors, infection spectrum, virulence determinants, biofilm formation, and metabolic adaptations of *Stenotrophomonas maltophilia*

Feature	Key findings	References
Risk factors	Immunocompromised state, malignancy, cystic fibrosis, immunosuppressive therapy, indwelling devices, and broad-spectrum antibiotic exposure.	[15], [27]
Infections	Pneumonia, bloodstream, wound, UTI, meningitis; frequent respiratory co-infections in critically ill COVID-19 patients.	[28], [32]
Virulence factors	Adhesion (pili, LPS, flagella), enzymes (proteases, lipases, DNases), motility, biofilm formation, quorum sensing, and iron acquisition systems.	[28], [30], [31]
Biofilm formation	Enhances persistence and resistance; key in device-related and chronic infections. Pili (smf-1, cbl) and gpmA influence biofilm development.	[29], [33]
Metabolic influence	Prefers amino acids over glucose; gpmA affects growth on amino acids, while glucose/ribose restores growth.	[29]

Abbreviations: *cbl*, chaperone/usher pilus gene cluster; COVID-19, coronavirus disease 2019; DNases, deoxyribonucleases; *gpmA*, phosphoglycerate mutase gene; LPS, lipopolysaccharide; *smf-1*, *Stenotrophomonas maltophilia* fimbrial protein 1 gene; UTI, urinary tract infection.

Notably, it has been revealed that *Stenotrophomonas maltophilia* protease 1 (StmPr1), the bacterium's key virulence factor—an excreted serine protease—has a unique self-cleavage that produces a shortened active form. Moreover, peptide-based inhibitors, particularly bortezomib, have been tested for their therapeutic potential. Using X-ray crystallography (1.64–2.08 Å), molecular dynamics, and small-angle X-ray scattering (SAXS), this research provides detailed insights into StmPr1's folding, stability, and resilience. This highlights the importance of the C-terminal extension and supports StmPr1 as a promising target for future drug development against *S. maltophilia* infections [27].

S. maltophilia in dogs with skin infections was examined for its virulence, biofilm formation, antibiotic resistance, and zoonotic risk. Fifteen isolates (5%) were identified from 300 skin swabs. All isolates were susceptible to TMP-SMX, fluoroquinolones, minocycline, and tigecycline but resistant to cefpodoxime and aztreonam. Multiple resistance genes, especially *qnr* (93.3%) and several β-lactamase genes, were detected, and all isolates showed high efflux activity. Most strains formed strong or moderate biofilms, carried key virulence genes, and exhibited high motility. The genetic profiles varied widely. These findings highlight the zoonotic potential of *S. maltophilia* in dogs and support the One Health approach to prevent the spread of multidrug-resistant virulent strains [34] .

Resistance mechanisms

S. maltophilia presents a significant clinical challenge due to its notable intrinsic and acquired resistance to multiple antibiotic classes [17]. This bacterium exhibits both chromosomally encoded intrinsic resistance and the capacity to acquire resistance through horizontal gene transfer or mutations, particularly under antibiotic selective pressure. Its ability to form biofilms, acquire resistance genes, and express multiple efflux pumps further contributes to its multidrug resistant (MDR) phenotype, thereby limiting the efficacy of conventional antimicrobial agents [35]. Consequently, managing *S. maltophilia* infections often necessitates meticulous antimicrobial selection and combination therapy, underscoring the urgent demand for innovative therapeutic strategies and enhanced infection control measures [36–38].

Resistance mechanisms in *S. maltophilia* encompass β-lactamase production, the presence of Qnr genes, class 1 integrons, and active efflux pumps. Class 1 integrons are particularly known for facilitating the acquisition and dissemination of resistance genes, notably impacting TMP-SMX, which is considered the first-line treatment. While other agents such as ceftazidime, ticarcillin-clavulanate, fluoroquinolones, and tetracyclines (e.g., tigecycline, minocycline, doxycycline) have shown efficacy, emerging resistance trends are a growing concern [17]. Beyond its inherent resistance determinants—including multidrug efflux pumps, β-lactamases, aminoglycoside-inactivating enzymes, and Qnr proteins—*S. maltophilia* continuously acquires novel resistance genes via horizontal gene transfer [39].

S. maltophilia demonstrates intrinsic resistance to most β-lactam antibiotics, primarily attributed to the production of two inducible β-lactamases: L1 and L2. The L1 enzyme, an Ambler class B metallo-β-lactamase, hydrolyzes nearly all β-lactams except aztreonam and is not inhibited by conventional β-lactamase inhibitors. Conversely, the L2 enzyme, an Ambler class A serine β-lactamase, efficiently hydrolyzes many cephalosporins and aztreonam but is susceptible to inhibition by serine β-lactamase inhibitors like clavulanic acid. This synergistic dual-enzyme system significantly contributes to the organism's broad-spectrum β-lactam resistance profile [40]. A study investigating antibiotic resistance genes in 250 clinical *S. maltophilia* isolates identified all isolates carried the L1 metallo-β-lactamase gene marker (*L1Q*) gene (100%), most harbored L2 serine β-lactamase gene marker (*L2Q*) (90%), and 15% possessed the aminoglycoside phosphotransferase (*Aph)* gene, indicating widespread β-lactamase and aminoglycoside resistance [41].

Resistance to TMP-SMX in *S. maltophilia* predominantly stems from mutations or genetic alterations in the *sul1* and sulfonamide-resistant dihydropteroate synthase 2 gene (*sul2)*,

which encode alternative forms of dihydropteroate synthase (DHPS), the target enzyme. These modified enzymes exhibit reduced binding affinity for sulfonamides, thereby diminishing TMP-SMX's inhibitory effect and allowing bacterial folate synthesis to persist [35].

A comprehensive analysis of *S. maltophilia* antibiotic resistance genes in 250 clinical isolates, employing biochemical characterization, Kirby–Bauer susceptibility testing, and polymerase chain reaction (PCR), revealed that all isolates carried the *L1Q* gene. Furthermore, 90% harbored the *L2Q* gene, associated with β-lactam resistance, and 15% possessed the *Aph* gene, linked to aminoglycoside resistance [41].

Whole-genome sequencing of 55 isolates collected over nine years has revealed extensive genetic diversity, identifying 22 new sequence types and six new genomospecies. Resistance to TMP-SMX was low (3.6%), and all isolates remained susceptible to minocycline. Common virulence genes identified included flagellar motor stator protein MotA gene (*motA*), *pilU*, *smf-1*, and Stenotrophomonas maltophilia protease 2 gene (*stmPr2*), with *S. maltophilia* and *S. pavanii* strains carrying the highest number of virulence factors [16].

The escalating threat of multidrug-resistant Gram-negative bacteria and the paucity of novel antibiotics have prompted a resurgence in the use of older drugs such as fosfomycin. *S.maltophilia* generally exhibits low susceptibility to many antibiotics. Unlike other bacteria, its fosfomycin resistance typically arises from mutations in central carbon metabolism enzymes rather than inactivation of the target or transporter proteins. Research indicates that *S. maltophilia* can develop high-level fosfomycin resistance under diverse conditions, with distinct mutations emerging depending on the environmental context, suggesting that resistance evolution pathways may vary by infection site [42].

A study conducted in an East China hospital further elucidated that resistance to sulfamethoxazole (SMX), frequently mediated by sulfonamide resistance gene family (*sul*) and trimethoprim-resistant dihydrofolate reductase A gene (*dfrA*) located within class 1 integrons, signified MDR. Evidence of clonal spread suggested cross-transmission of resistant strains, emphasizing the critical need for enhanced infection control measures [43].

Moreover, *S. maltophilia* generally exhibits low susceptibility to synthetic antimicrobial agents, including quinolones. Quinolone resistance is multifactorial, often resulting from the synergistic action of active efflux pumps, which expel the antibiotic from the bacterial cell, and the presence of the *Stenotrophomonas maltophilia* quinolone resistance protein (SmQnr), a plasmid-mediated quinolone resistance determinant. SmQnr protects DNA gyrase and topoisomerase IV—key targets of quinolones—from the drug's inhibitory effects, further contributing to resistance. Collectively, these mechanisms underscore the complex and adaptive nature of *S. maltophilia* resistance to multiple antibiotic classes [44].

A previously unrecognized multidrug resistance mechanism has been identified in *S. maltophilia*, inducible by tetracycline exposure. This resistance originates from an active efflux system that expels tetracycline from the cell, also conferring cross-resistance to quinolones and chloramphenicol, but not to aminoglycosides or β-lactam antibiotics. This MDR phenotype is associated with the expression of an outer membrane protein (OMP54), observed in both experimental models and clinical MDR isolates [45].

A study from Maharaj Nakorn Chiang Mai Hospital, Thailand (2015–2016), analyzed 200 clinical isolates, primarily from sputum. It found that infections were more prevalent in older male patients with underlying conditions and a history of invasive procedures. The isolates demonstrated the highest resistance to ceftazidime, while minocycline remained effective. Common resistance genes included resistance–nodulation–division-family multidrug efflux transporter SmeF gene (*smeF*) (91.5%), L1 metallo-β-lactamase gene (*blaL1*) (43%), and L2 serine β-lactamase gene (*blaL2*) (10%). Most isolates formed biofilms, produced hemolysin, and exhibited motility. Multilocus sequence typing revealed high genetic diversity, with 141 sequence types, including 130 novel ones. This study highlights significant variation in virulence and resistance traits, emphasizing the need for improved control and prevention strategies in Thailand [46]. More recently, experimental evolution and whole-genome sequencing were employed to track genetic mutations driving resistance. Key findings revealed mutations in SmeDEF multidrug efflux pump transcriptional repressor gene (*smeT*) and redox-sensitive transcriptional activator SoxR gene (*soxR*) for ciprofloxacin resistance, 50S ribosomal protein L1 gene (*rplA*) for tobramycin, and dihydropteroate synthase gene (*folP*) and SmeVWX multidrug efflux pump regulator gene (*smeRv*) for SMX. These results underscore *S. maltophilia*'s remarkable adaptability and the urgent need for alternative treatments [47].

Treating *S. maltophilia* infections is challenging due to its intrinsic resistance to numerous antibiotics and its propensity to acquire new resistances via mutations and horizontal gene transfer. Resistance to commonly used agents, including quinolones, TMP-SMX, and cephalosporins, has emerged. Genomic analyses have identified numerous resistance genes, primarily encoding inactivating enzymes and efflux pumps. Additionally, non-typical mechanisms, such as metabolic genes, biofilm formation, and persistence, also contribute to phenotypic resistance. Furthermore, complete genome sequencing of clinical (K279a, D457) and environmental strains (R551-3, JV3) reveals conserved genomic features, aiding in the identification of antibiotic resistance determinants [35].

Whole-genome sequencing and phylogenetic analysis have revealed no clear correlation between strain origin and resistance level. Genome data identified multiple resistance genes and efflux pumps, with 57% being newly reported. Notably, two environmental strains lacked the typical resistance–nodulation–division (RND) efflux pump (SmeABC) but harbored a novel efflux system (EbyCAB), likely acquired through horizontal gene transfer [48].

A *S.maltophilia* strain carrying the Verona integron-encoded metallo-β-lactamase 1 gene (*blaVIM-1*) and resistant to TMP-SMX was isolated from a rectal surveillance swab. Genetic analysis revealed a 91 kb integrative and conjugative element

Table 3. Key characteristics, antibiotic resistance profiles, and genetic diversity of *Stenotrophomonas maltophilia*

Category	Key findings	References
Global prevalence	Rising prevalence: 0.8–1.4% (1997–2003) → 1.3–1.68% (2007–2012); found in both hospital and community settings.	[15]
Intrinsic resistance	Low membrane permeability, efflux pumps (SmeABC, EbyCAB), chromosomal β-lactamases (L1, L2), and SmQnr-mediated quinolone protection.	[35], [40], [44], [48]
Acquired resistance	Horizontal gene transfer (integrons, ICEs), mutations in sul1/sul2, smeT, soxR, rplA, folP; acquisition of resistance genes (e.g., blaVIM-1, sul1, aac).	[35], [39], [47], [49]
Key antibiotic resistance	Resistance to β-lactams, TMP-SMX, quinolones, tetracyclines; reduced susceptibility to fosfomycin.	[15], [42], [44], [47]
Resistance mechanisms	Enzymatic degradation, efflux activity, target mutations, metabolic adaptation, and biofilm-associated tolerance.	[35], [40], [42], [44]
Genetic diversity	High heterogeneity: multiple sequence types and genomospecies; virulence genes (motA, pilU, smf-1, stmPr2); no clear link between origin and resistance.	[13], [48]

Abbreviations: *aac*, aminoglycoside acetyltransferase gene; *blaVIM-1*, Verona integron-encoded metallo-β-lactamase 1 gene; EbyCAB, EbyCAB multidrug efflux pump system; *folP*, dihydropteroate synthase gene; ICEs, integrative and conjugative elements; L1, L1 metallo-β-lactamase; L2, L2 serine β-lactamase; *motA*, flagellar motor protein A gene; *pilU*, type IV pilus biogenesis protein gene; *rplA*, 50S ribosomal protein L1 gene; SmeABC, SmeABC multidrug efflux pump system; *smeT*, SmeDEF efflux pump repressor gene; *smf-1*, *Stenotrophomonas maltophilia* fimbrial protein 1 gene; SmQnr, *Stenotrophomonas maltophilia* quinolone resistance protein; *soxR*, oxidative stress response transcriptional regulator gene; *stmPr2*, extracellular serine protease gene; *sul1/sul2*, sulfonamide resistance genes 1 and 2; TMP-SMX, trimethoprim-sulfamethoxazole.

(ICE) containing multiple resistance genes (*sul1*, *blaVIM-1*, *aac(6')-Ib*, *aac(6')-31*, *qacEΔ1*, *cld*, *merEDAPTR*), similar to clc-type ICEs found in *Pseudomonas aeruginosa*. These findings suggest horizontal gene transfer of resistance elements from *pseudomonads* to *S. maltophilia*, facilitating the dissemination of multidrug resistance [49].

It has also been observed that stress conditions can induce temporary phenotypic resistance. Consequently, therapeutic options are limited, necessitating novel antimicrobials or efflux pump inhibitors to enhance treatment outcomes [50].

The characteristics, resistance mechanisms, and genetic diversity of *S. maltophilia* are summarized in Table 3.

Treatment options and novel therapies for *S. maltophilia*

S. maltophilia is an emergent pathogen responsible for respiratory, bloodstream, and urinary tract infections. Its intrinsic and acquired multidrug resistance, driven by low membrane permeability, efflux pumps, and β-lactamases, severely constrains therapeutic options. The absence of standardized susceptibility testing further complicates treatment [51]. TMP-SMX remains the first-line agent, with minocycline, ticarcillin-clavulanate, fluoroquinolones, and tigecycline serving as alternatives [51].

Established clinical therapies

Current clinical guidelines endorse TMP-SMX as the standard first-line therapy for susceptible S. maltophilia infections. Minocycline and fluoroquinolones are critical alternative agents when TMP-SMX is precluded by resistance, intolerance, or contraindications. For severe infections caused by MDR isolates, newer agents such as cefiderocol and ceftazidime-avibactam plus aztreonam (CZA-ATM) show promise, though their optimal clinical role requires further elucidation [52]. In contrast, a systematic review of 24 studies reported that fluoroquinolones and potentially tetracyclines were associated with lower mortality rates than TMP-SMX. Monotherapy appeared more protective than combination therapy, although this difference was not statistically significant [53].

Despite increasing resistance, TMP-SMX remains a common drug of choice. Alternatives such as tigecycline, minocycline, doxycycline, and fluoroquinolones exhibit variable efficacies, while combination and novel therapies are under investigation [17]. When comparing minocycline, tigecycline, and eravacycline, susceptibility to tetracyclines generally remains preserved, even in the presence of TMP-SMX and quinolone resistance. *In vitro* minimum inhibitory concentration (MIC) data indicate that minocycline and eravacycline demonstrate slightly superior activity to tigecycline. However, all three agents show favorable sensitivity profiles, with MIC_{90} values below 2 μg/mL for over 90% of *S. maltophilia* isolates. Consequently, minocycline is recommended as the preferred treatment, except in polymicrobial infections where tigecycline or eravacycline may offer broader coverage [54].

A recent meta-analysis, encompassing 289 studies identified through a systematic search of PubMed, Embase, Web of Science, and Scopus (up to May 2023), assessed global antibiotic resistance patterns of *S. maltophilia* to inform treatment strategies. The highest resistance rates were observed for doripenem (97%), cefoxitin (96%), and imipenem (95%), whereas minocycline (3%) and cefiderocol (4%) showed the lowest resistance. Resistance to TMP-SMX remained stable at approximately 14% after 2010. Minocycline and cefiderocol appear to be the most promising options, with TMP-SMX remaining an effective first-line therapy [55].

Treatment challenges persist due to the limited number of effective drugs, unreliable susceptibility testing, and the absence of standardized United States Food and Drug Administration (FDA) breakpoints. Although levofloxacin

demonstrates efficacy comparable to TMP-SMX, rapid resistance can develop. Minocycline exhibits potent *in vitro* activity, but clinical evidence is limited. Novel agents like cefiderocol show promise but require further validation. Combination therapies are frequently employed despite insufficient supporting data [56].

A pharmacokinetic/pharmacodynamic approach, utilizing Monte Carlo simulations, assessed the effectiveness of TMP-SMX, levofloxacin, minocycline, tigecycline, cefiderocol, and aztreonam-avibactam against *S. maltophilia* in critically ill patients. Cefiderocol, minocycline, tigecycline, and aztreonam-avibactam achieved the best target attainment for empirical therapy, while TMP-SMX was more effective against U.S. isolates [57]. Although TMP-SMX is the primary treatment for confirmed *S. maltophilia* infections, caution is warranted when interpreting isolates, as the organism may represent colonization rather than true invasive disease, particularly in respiratory samples and indwelling devices. Therefore, treatment decisions should integrate clinical, microbiological, and radiological evidence.

While TMP-SMX is the primary treatment for *S. maltophilia*, alternative options are crucial when resistance or intolerance occurs. A review of 31 case reports and five case series involving 49 patients reported cure or improvement rates of 90% with ciprofloxacin-based therapy, 75% with ceftriaxone- or ceftazidime-based regimens, and 66.7% with ticarcillin- or ticarcillin-clavulanate-based regimens. These findings suggest that these agents, alone or in combination, may serve as potential alternatives to TMP-SMX [58] (Table 4, Figure 1).

Emerging clinical and advanced therapeutic options

S. maltophilia isolates were tested against various antibiotics, including β-lactam-β-lactamase inhibitor combinations, cefiderocol, quinolones, and tetracyclines, using the broth microdilution method. Whole-genome sequencing was performed on cefiderocol-resistant strains to identify resistance genes and phylogenetic relationships. Among 101 isolates, TMP-SMX (99%), levofloxacin (95%), and minocycline (100%) showed the highest susceptibility, while ceftazidime showed the lowest (77%). Five isolates were resistant to cefiderocol (MIC $\geq$ 2 μg/mL). Meropenem-vaborbactam and imipenem-relebactam were ineffective, whereas CZA-ATM enhanced ceftazidime activity. Genomic analysis revealed resistance genes, including MDR efflux pumps and β-lactamases. Although new β-lactamase inhibitors show limited activity, avibactam and cefiderocol may offer therapeutic potential, with tetracyclines demonstrating the strongest *in vitro* efficacy [59].

Eravacycline and omadacycline, novel tetracyclines, show promise as treatment options for *S. maltophilia*. While eravacycline's pharmacokinetic/pharmacodynamic profile is similar to tigecycline, potentially limiting its effectiveness against bloodstream infections, it exhibits notable antibacterial potency and a broad spectrum of activity. Conversely, omadacycline has demonstrated *in vitro* efficacy, though its MIC values are generally higher compared to other tetracycline derivatives [60, 61].

Resistance to agents such as ceftazidime, ticarcillin-clavulanate, and fluoroquinolones is increasing. Tetracyclines (tigecycline, minocycline, and doxycycline) maintain strong activity. Current research explores combination therapies, new agents, and aerosolized antibiotics for *S. maltophilia* infections [17]. Additionally, a retrospective study (2010–2016) compared clinical outcomes of adult patients receiving monotherapy with TMP-SMX, fluoroquinolones, and minocycline. Among 284 patients (TMP-SMX = 217, fluoroquinolone = 28, minocycline = 39), rates of clinical failure and 30-day mortalities were comparable across groups. After adjustment, minocycline was associated with lower mortality compared to TMP-SMX. These findings suggest that alternatives such as minocycline may provide equal or superior outcomes, implying that TMP-SMX may no longer be the optimal monotherapy for *S. maltophilia* infections [62].

Colistin is often reserved as salvage therapy for MDR Gram-negative infections, but its use is limited by nephrotoxicity, reduced efficacy, and the availability of safer alternatives. In *S. maltophilia*, susceptibility testing is challenging due to complex adaptive resistance mechanisms that often emerge upon drug exposure. Reported *in vitro* susceptibility rates range from 9% to 86% and typically require high drug concentrations. Combination therapy shows promise, with synergistic effects observed for colistin paired with N-acetylcysteine, telavancin, rifampicin, or TMP-SMX. Notably, the colistin–rifampin combination has demonstrated consistent bactericidal activity *in vitro* and in experimental models [63–66] (Table 4, Figure 1).

Novel therapeutic approaches

The first discovery of two novel modular bacteriocins, SmaltM and SmaltM2, from *S. maltophilia* is noteworthy. These peptidoglycan-degrading bacteriocins, cloned and transiently expressed in tobacco plants, exhibited potent antibacterial activity against *S. maltophilia* strains. Stenocins represent promising alternatives to conventional antibiotics for controlling MDR *S. maltophilia* infections [67]. Furthermore, the synergistic and anti-biofilm effects of ceragenins (CSA-13, CSA-44, and CSA-131) with ceftazidime, levofloxacin, TMP-SMX, and colistin against clinical *S. maltophilia* strains have been evaluated using MIC/minimum bactericidal concentration (MBC) tests, killing assays, and crystal violet staining.

Ceragenins demonstrate strong antibacterial and anti-biofilm activities, with synergistic effects when combined with certain antibiotics. Ceragenins hold promise as potential *in vitro* therapeutic agents, either alone or in combination with conventional antibiotics, for the treatment of *S. maltophilia* infections [68] (Table 4, Figure 1).

Natural and plant-derived compounds

Epigallocatechin-3-gallate (EGCG), a catechin derived from green tea, was evaluated for its efficacy against 40 clinical isolates of *S. maltophilia*. The compound exhibited $MIC_{50/90}$ values of 256–512 mg/L and $MBC_{50/90}$ of 512 mg/L. Time-kill assays indicated a slow bactericidal effect, achieving a 2.5 log reduction within 24 h. These promising *in vitro* results

Table 4. Summary of current and emerging therapeutic options for *Stenotrophomonas maltophilia*, including antibiotic agents, novel compounds, natural products, and bacteriophages

Category	Agent / approach	Key findings	References
First-line therapy	TMP-SMX	Standard treatment; still effective in most cases, though resistance is emerging; limited PK/PD correlation.	[51], [52], [55], [56], [62]
Fluoroquinolones	Levofloxacin, ciprofloxacin	Effective alternative; comparable to TMP-SMX; resistance may develop; ~90% clinical improvement reported for ciprofloxacin.	[53], [56], [58]
Tetracyclines	Minocycline, tigecycline, doxycycline, eravacycline, omadacycline	Minocycline most active (MIC_{90} <2 μg/mL); eravacycline highly potent; useful in polymicrobial infections.	[54], [15], [60], [61], [62]
New β-lactams	Cefiderocol; CZA + aztreonam	Cefiderocol shows low resistance (~4%); CZA–ATM effective against MBL producers; most β-lactams remain limited.	[52], [55], [57], [59]
Other β-lactams	Ticarcillin–clavulanate, cephalosporins	Moderate clinical response (66–75%); declining susceptibility reported.	[58], [59]
Colistin	Alone or in combinations	Salvage therapy; variable susceptibility (9–86%); synergy with rifampin, NAC, and TMP-SMX.	[63–66]
Natural compounds	EGCG, essential oils (citral, rose oil)	Antibacterial and membrane-disrupting activity; strong *in vitro* efficacy.	[69], [7 0], [74]
Novel agents	PYED-1, gepotidacin	Reduce biofilm and resistance; demonstrate *in vivo* activity and improved survival.	[71], [72]
Efflux inhibitors	Plant extracts, emodin	Restore antibiotic activity; up to 8-fold MIC reduction observed.	[73]
Bacteriocins	Stenocins	Potent antimicrobial activity; promising alternative therapeutic class.	[67]
Phage therapy (single)	Individual lytic phages	Effective against MDR strains and biofilms; improved survival in animal models; broad host range.	[76–86]
Phage therapy (cocktails)	Multi-phage combinations	Broader coverage (>50% strains); sustained suppression (>48 h); higher efficacy than monotherapy.	[77]
Antimicrobial peptides	ε-poly-L-lysine	Active against MDR pathogens; synergistic effects with phages.	[79]

This table outlines each agent's type, mechanism of action, key efficacy findings, and supporting references. It summarizes both established treatments and promising experimental approaches for managing *S. maltophilia* infections. The therapeutic strategies presented are supported by varying levels of evidence. This includes clinical studies (e.g., TMP-SMX, fluoroquinolones, tetracyclines, cefiderocol, CZA-ATM, other β-lactams, and colistin), *in vitro* investigations (e.g., natural compounds, efflux inhibitors, bacteriocins, and antimicrobial peptides), animal studies (e.g., novel agents and phage therapy), and combinations of preclinical and computational evidence. Consequently, the strength of evidence differs among the listed approaches. **Abbreviations:** ATM, aztreonam; CZA, ceftazidime-avibactam; EGCG, epigallocatechin-3-gallate; MBL, metallo-β-lactamase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MIC_{90}, minimum inhibitory concentration required to inhibit 90% of isolates; NAC, N-acetylcysteine; PK/PD, pharmacokinetic/pharmacodynamic; *S. maltophilia*, *Stenotrophomonas maltophilia*; TMP-SMX, trimethoprim-sulfamethoxazole.

suggest that EGCG warrants further investigation into its mechanism of action and potential application in combination therapies [69].

In a separate study, seven essential oils were tested against *S. maltophilia*, a multidrug-resistant pathogen and common food spoilage bacterium. *Litsea cubeba* oil (LCO) demonstrated the most potent antibacterial activity, with an MBC of 0.125% (v/v), and effectively inhibited bacterial growth in fumigation tests. Citral, the primary active compound in LCO, was found to induce membrane damage and rupture, with MIC and MBC values of 0.25% and 0.5% (v/v), respectively. These findings underscore the potential of LCO and citral as natural alternatives for controlling resistant *S. maltophilia* in food systems [70] (Table 4, Figure 1).

Anti-virulence and adjunctive approaches

A previous investigation assessed the antibacterial properties of the corticosteroid deflazacort and its precursors. While most compounds showed no activity against the reference *S. maltophilia* strain, PYED-1 exhibited weak activity against certain clinical isolates and demonstrated *in vitro* synergism with aminoglycosides. At sub-inhibitory concentrations, PYED-1 reduced biofilm formation and downregulated genes associated with virulence and aminoglycoside resistance, suggesting its potential as an adjuvant therapeutic agent [71].

The novel antimicrobial gepotidacin, a triazaacenaphthylene topoisomerase inhibitor, was tested against 100 *S. maltophilia* isolates. Gepotidacin displayed MIC values ranging from 0.25–16 mg/L (MIC_{50}: 2 mg/L; MIC_{90}: 8 mg/L), with

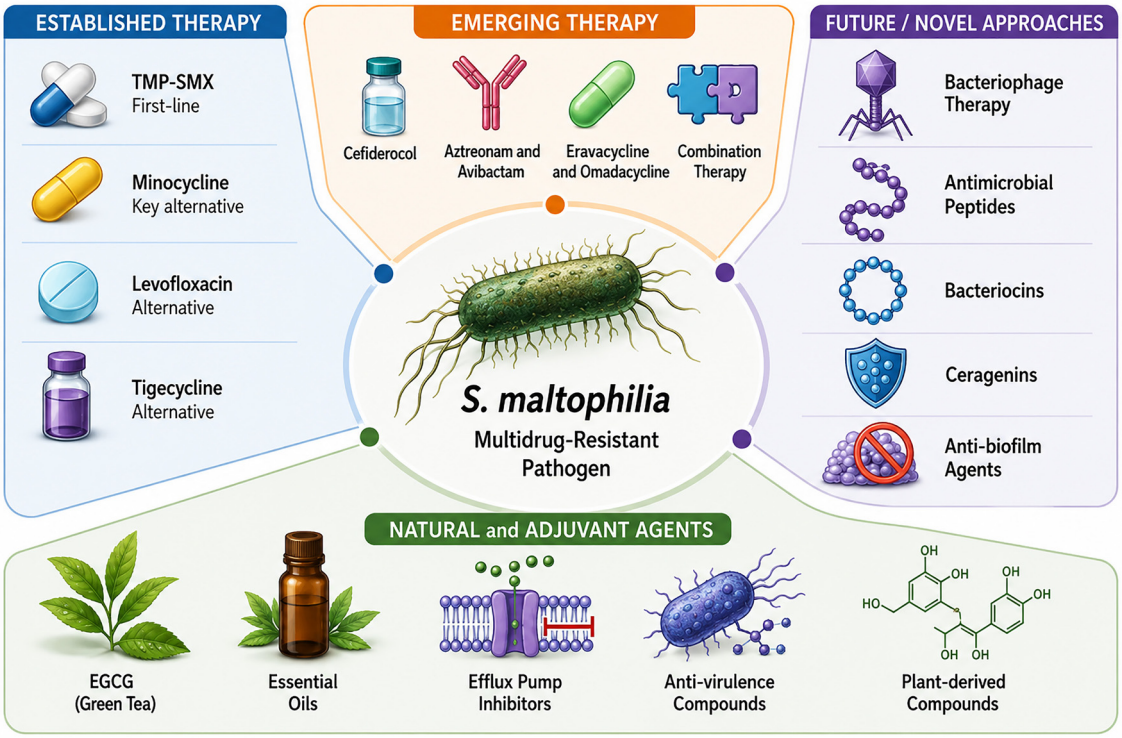


Figure 1. Current and emerging therapeutic strategies for *Stenotrophomonas maltophilia* infections. The figure summarizes established, emerging, natural/adjuvant, and future therapeutic approaches for the management of multidrug-resistant *S. maltophilia* infections. Established therapies include trimethoprim-sulfamethoxazole as the first-line option, with minocycline as a key alternative and levofloxacin or tigecycline as additional treatment options. Emerging therapies include cefiderocol, ceftazidime-avibactam plus aztreonam, newer tetracyclines such as eravacycline and omadacycline, and combination therapy, particularly for resistant or severe infections. Natural and adjuvant approaches include epigallocatechin-3-gallate, essential oils, efflux pump inhibitors, anti-virulence compounds, and other plant-derived compounds. Future and novel strategies include bacteriophage therapy, antimicrobial peptides, bacteriocins, ceragenins, and anti-biofilm agents, which may be particularly relevant for multidrug-resistant and biofilm-associated infections. While established antibiotics are supported by clinical experience, most emerging and novel approaches remain based primarily on *in vitro*, experimental, or preclinical evidence and require further clinical validation. **Abbreviations:** ATM, aztreonam; CZA, ceftazidime-avibactam; EGCG, epigallocatechin-3-gallate; *S. maltophilia*, *Stenotrophomonas maltophilia*; TMP-SMX, trimethoprim-sulfamethoxazole.

its activity independent of TMP-SMX resistance. Time-kill assays revealed strain- and time-dependent bactericidal effects. *In vivo* testing using *G. mellonella* larvae demonstrated improved survival rates (61%–90%). These results highlight gepotidacin's promising antimicrobial potential against *S. maltophilia* [72].

Plants exposed to metal contaminants produce secondary metabolites capable of modulating MDR by inhibiting bacterial efflux pumps and consequently lowering antibiotic MICs. The effects of belowground metabolites from *Pteris vittata* L. and *Fallopia japonica*, two metal-tolerant plants from northern Vietnam, were examined against six efflux pump-mediated antibiotic-resistant *S. maltophilia* strains. Chemical profiles of aqueous and dichloromethane (DCM) extracts were analyzed using ultrahigh-performance liquid chromatography coupled to diode-array detection, electrospray ionization, and quadrupole time-of-flight mass spectrometry (UHPLC-DAD-ESI/QTOF). The DCM extract of *F. japonica* showed the strongest antibacterial effect (MIC: 31.25 μg/mL) and significantly reduced gentamicin MICs by up to eight-fold. Emodin, the major compound, exhibited moderate activity. These findings suggest that *F. japonica* root extracts, particularly their DCM fraction, may serve as promising sources of novel efflux pump inhibitors [73].

The antibacterial mechanism of rose essential oil (REO) was investigated *in vitro* against *S. maltophilia*, positioning it as a natural, safe, and eco-friendly agent. REO treatment induced significant cell damage and content leakage, as evidenced by scanning and transmission electron microscopy. Metabolomic analysis revealed disruptions in amino acid, nucleotide, and aminoacyl-tRNA biosynthesis pathways. These findings elucidate the inhibitory mechanism of REO and support its potential as a natural food preservative [74].

An *in vitro* study aimed to identify natural inhibitors targeting the bacterial L1 β-lactamase enzyme, which confers resistance to β-lactam antibiotics. Computational tools, including virtual screening, molecular docking, and molecular dynamics simulations, were employed to analyze phytochemicals from the Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT) database for their inhibitory potential. Among the screened compounds, withanolide R demonstrated the strongest binding affinity and stability with L1 β-lactamase, suggesting its promise as a natural inhibitor to combat *S. maltophilia* resistance [75] (Table 4, Figure 1).

Phage therapy and antimicrobial peptides

Phage therapy, particularly in combination with antibiotics, offers a promising alternative treatment strategy. The bacteriophage StM171, isolated from hospital wastewater, was characterized by a medium host range, low burst size, and moderate lytic activity. Genomic analysis (44 kbp, 59 open reading frames [ORFs]) classified StM171 into a new putative *Nordvirus* genus, alongside phages Suso and HXX_Dennis. *S. maltophilia* mutants resistant to StM171 displayed altered antibiotic sensitivity, regaining susceptibility to β-lactams but developing resistance to erythromycin. StM171 also exhibited strain- and antibiotic-dependent effects on biofilm formation [76].

For an alternative therapeutic approach, 18 phages were isolated from Southern California wastewater and tested *in vitro* against *S. maltophilia* strain B28B. Three genetically distinct phages were selected to form a cocktail, which significantly suppressed bacterial growth over 48 h compared to individual phages. This cocktail also infected over 50% of the 46 tested *S. maltophilia* strains and showed enhanced efficacy against 6 clinically relevant isolates. These results highlight the potential of multi-phage cocktails as a promising therapeutic strategy for treating resistant *S. maltophilia* infections [77].

Bacteriophages are promising biological control agents for multidrug-resistant bacteria. Another study characterized a novel lytic phage, vB_SmaS_QH3, isolated from hospital sewage using *S. maltophilia* strain no. 3738. Transmission electron microscopy revealed its classification within the *Caudoviricetes*, possessing an icosahedral head and a long tail. Despite a narrow host range, vB_SmaS_QH3 displayed cross-genus activity against *S. maltophilia* and *Pseudomonas aeruginosa*. *In vitro*, it inhibited bacterial growth within 9 h, and *in vivo*, it significantly improved *G. mellonella* survival. Overall, vB_SmaS_QH3 demonstrated strong antibacterial potential and stability, making it a promising therapeutic candidate [78].

An *in vitro* study isolated cationic metabolite-producing bacteria from soil samples, identifying them as *S. maltophilia* HS4 and *Paenibacillus polymyxa* HS5 based on biochemical tests and 16S rRNA analysis. The purified cationic peptide, identified as ε-poly-L-lysine using high-performance liquid chromatography (HPLC), sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), and Fourier-transform infrared spectroscopy (FTIR), exhibited strong antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Serratia marcescens*, and *Klebsiella pneumoniae*. Furthermore, ε-poly-L-lysine combined with specific bacteriophages enhanced activity against vancomycin-resistant *E. faecalis* and colistin-resistant *K. pneumoniae*. These findings suggest that ε-poly-L-lysine from these novel strains could serve as a promising antimicrobial agent against multidrug-resistant pathogens [79].

A novel lytic phage, vB_SmaS_QH16, was isolated from hospital sewage and characterized for its antibacterial activity. This phage, belonging to the *Caudoviricetes*, possesses a 43.5 kb genome with 64 ORFs and lacks virulence or resistance genes. It lysed 47.9% of tested *S. maltophilia* strains, exhibited optimal activity at an multiplicity of infection (MOI) of 0.01, and remained stable across temperatures of 4–50 °C and pH 3–11. vB_SmaS_QH16 effectively inhibited and eradicated biofilms in a dose-dependent manner and significantly improved survival rates in *G. mellonella* and mouse models. These findings highlight its strong therapeutic potential as a safe, stable, and effective alternative for *S. maltophilia* infections, warranting further studies on the mechanisms of resistance and biofilm disruption [80].

Furthermore, a novel lytic bacteriophage, AXL3 (vB_SmaS-AXL_3), was isolated from soil and characterized. AXL3 infected 5 of 29 clinical isolates and was identified by electron microscopy as a member of the *Siphoviridae* family. Genome sequencing revealed a 47.5 kb genome encoding 65 proteins with no lysogeny-associated genes. AXL3 utilizes the bacterial type IV pilus as its receptor, confirming its virulence. These findings suggest that AXL3 is a promising phage therapy candidate with the potential for genetic modifications to expand its host range [81].

Additionally, a novel bacteriophage, BUCT609, was isolated from hospital sewage using *S. maltophilia* strain No. 3015 as the host and characterized. Electron microscopy revealed its classification within the *Podoviridae* family, featuring a ~50 nm capsid and a 10 nm tail. Phage BUCT609 demonstrated a short latent period (10 min), a large burst size (382 PFU/cell), and strong stability across pH 3–10 and temperatures 4–55 °C. Its 43,145 bp genome (58% GC) lacked virulence or antibiotic resistance genes and shared less than 45% similarity with known phages. *In vivo*, phage treatment significantly improved the survival of *S. maltophilia*-infected mice, indicating BUCT609's potential as a therapeutic agent against *S. maltophilia* infections [82].

A novel bacteriophage, BUCT700, possessing a 43,214 bp double-stranded DNA genome (70% GC) with 55 ORFs and no virulence or resistance genes, was identified. It rapidly adsorbs onto *S. maltophilia* via the PilX receptor and efficiently produces new virions. *In vivo*, BUCT700 increased the survival rate of infected *G. mellonella* larvae from 0% to 100% within 72 h, particularly when used prophylactically. These findings highlight BUCT700 as a promising candidate for the prevention and treatment of *S. maltophilia* infections, especially those associated with medical devices [83].

BUCT603, which targets drug-resistant *S. maltophilia*, infected 10 of 15 *S. maltophilia* strains using the TonB energy-transducing protein (TonB) as its receptor, inhibited bacterial growth within 1 hour *in vitro*, and significantly improved mouse survival rates. These results indicate BUCT603's strong potential as a therapeutic option against *S. maltophilia* infections [84].

A new *Siphoviridae* phage, DLP3, was isolated from soil and identified as the second member of the *Delepquintavirus* genus, exhibiting one of the broadest host ranges among *S. maltophilia* phages (infecting 22/29 strains). Although temperate, DLP3 infects via the Type IV pilus and demonstrates strong lytic activity *in vivo*. With genetic modifications to eliminate lysogeny, DLP3 holds significant therapeutic potential against *S. maltophilia* infections [85].

A novel *Siphoviridae* bacteriophage, vB_SmaS_BUCT626, was isolated and demonstrated strong lytic activity against 10 of 20 *S. maltophilia* strains. The phage remained stable across broad temperature (4–70 °C) and pH (3–13) ranges and was chloroform-tolerant. Its 61,662 bp genome (56.2% GC) encodes 100 ORFs without resistance, toxin, or lysogenic genes, indicating its potential as a promising biocontrol agent against *S. maltophilia* infections [86]. (Table 4, Figure 1).

Discussion

S. maltophilia has emerged as a clinically significant opportunistic pathogen due to its intrinsic resistance mechanisms and increasing prevalence in healthcare settings. TMP-SMX is currently recommended as the first-line treatment, supported by evidence from this study. Minocycline, fluoroquinolones, and newer agents such as cefiderocol serve as alternatives for resistant infections or in patients intolerant to TMP-SMX [52, 55]. Recent studies demonstrate excellent *in vitro* activity and low resistance rates for minocycline and cefiderocol [54, 55]. Furthermore, cefiderocol, minocycline, tigecycline, and aztreonam-avibactam may offer favorable pharmacokinetic/pharmacodynamic profiles, particularly in critically ill patients [57].

Despite these advancements, several uncertainties persist. While numerous studies report promising *in vitro* results for novel tetracyclines, β-lactam-β-lactamase inhibitor combinations, bacteriophages, bacteriocins, ceragenins, and plant-derived compounds, clinical evidence supporting their routine use remains limited [59–61, 67, 68]. Most data originate from laboratory investigations, animal models, case reports, or small retrospective studies, which restrict the ability to draw definitive conclusions regarding long-term safety, efficacy, and optimal dosing. Although phage therapy shows promise in experimental models, standardized clinical protocols and large-scale human studies are lacking [76–86].

A crucial distinction must be made between infection and colonization. *S. maltophilia* is frequently isolated from respiratory specimens, indwelling devices, and hospitalized patients, where colonization may occur without active infection. Therefore, antimicrobial treatment should be guided by clinical presentation, radiological findings, and microbiological evidence, rather than solely by culture results [57].

The current literature also presents several limitations. Significant heterogeneity exists among studies concerning patient populations, infection sites, susceptibility testing methodologies, and outcome definitions. Regional variations in antimicrobial resistance patterns further impact the generalizability of findings across geographical settings. Additionally, evolving susceptibility breakpoints and testing recommendations for *S. maltophilia* make comparisons between older and more recent studies challenging [56]. Finally, many emerging therapies have been evaluated primarily through *in vitro* experiments, hindering their translation to clinical practice.

In summary, the available evidence supports TMP-SMX and minocycline as primary therapeutic options, with cefiderocol and other emerging agents showing promising results. To establish evidence-based treatment strategies for S. maltophilia, well-designed prospective clinical trials, standardized susceptibility testing methods, and multicenter investigations are urgently needed to validate the clinical utility of novel therapeutic approaches.

Conclusion

S. *maltophilia* is an opportunistic, multidrug-resistant, Gram-negative bacterium increasingly implicated in both hospital- and community-acquired infections, particularly in immunocompromised patients. This pathogen persists in diverse environments, including soil, water, and hospital devices such as catheters, ventilators, and waterlines, with biofilm formation facilitating its survival and transmission. Outbreaks in ICUs have been linked to contaminated sinks and drinking water devices, underscoring the importance of stringent infection control measures. Its pathogenesis involves adhesion, pili, flagella, lytic enzymes, quorum sensing, and metabolic adaptability, all contributing to chronic device-associated infections. Increasing prevalence and mortality have been reported in various healthcare settings, though trends exhibit regional and study-design variability. Treatment poses challenges due to intrinsic and acquired resistance, with TMP-SMX remaining the first-line therapy. Alternatives include minocycline, tigecycline, fluoroquinolones, and newer agents such as cefiderocol. Emerging strategies, including bacteriophages, bacteriocins, ceragenins, plant-derived compounds, and antibiofilm agents, have demonstrated promising results in experimental and preclinical studies, although further clinical validation is essential. Vigilant surveillance, robust antibiotic stewardship, and continued research into novel therapeutic approaches are critical to improving the management of this emerging pathogen.

Conflict of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Submitted: 17 April 2026
Accepted: 08 July 2026
Published online: 12 August 2026

References

[1] Mikhailovich VM, Heydarov RN, Bocharova JA, Chebotar IV. Molecular-genetic portrait of virulence of Stenotrophomonas maltophilia. Zh Mikrobiol Epidemiol Im zmunobiol 2023;100(5):380–90. https://doi.org/10.36233/0372-9311-417

[2] Mukherjee P, Roy P. Genomic potential of Stenotrophomonas maltophilia in bioremediation with an assessment of its multifaceted role in our environment. Front Microbiol 2016;7:967. https://doi.org/10.3389/fmicb.2016.00967

[3] Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. Clin Microbiol Rev 2012;25(1):2–41. https://doi.org/10.1128/CMR.00019-11

[4] Gawande R, Sande S. Stenotrophomonas maltophilia: a threatening nosocomial pathogen. J Sci Soc 2024;51(4):505–10. https://doi.org/10.4103/jss.jss_59_24

[5] Biagi M, Tan X, Wu T, Lee M, Patel S, Butler D, et al. Activity of potential alternative treatment agents for Stenotrophomonas maltophilia isolates nonsusceptible to levofloxacin and/or trimethoprim-sulfamethoxazole. J Clin Microbiol 2020;58(2). https://doi.org/10.1128/JCM.01603-19

[6] Ryan RP, Monchy S, Cardinale M, Taghavi S, Crossman L, Avison MB, et al. The versatility and adaptation of bacteria from the genus Stenotrophomonas. Nat Rev Microbiol 2009;7(7):514–25. https://doi.org/10.1038/nrmicro2163

[7] Cristina ML, Spagnolo AM, Sartini M, Schinca E, Ottria G, Perdelli F, et al. Stenotrophomonas maltophilia outbreak in an ICU: investigation of possible routes of transmission and implementation of infection control measures. Pathogens 2024;13(5):369. https://doi.org/10.3390/pathogens13050369

[8] Wang H, Zhang Y, Wang X, Liu Y, Chen M, Li Y, et al. Epidemiology and antimicrobial resistance of Stenotrophomonas maltophilia in China, 2014–2021. Infect Dis Ther 2025;14(1):261–74. https://doi.org/10.1007/s40121-024-01099-7

[9] Costa S, Oliveira A, Silva M, Ferreira R, Sousa J, Santos L, et al. Determinants of clinical cure and mortality in patients with Stenotrophomonas maltophilia infections: a retrospective analysis. Cureus 2025;17. https://doi.org/10.7759/cureus.86294

[10] Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with Stenotrophomonas maltophilia. Clin Microbiol Rev 1998;11(1):57–80. https://doi.org/10.1128/CMR.11.1.57

[11] Cervia JS, Ortolano GA, Canonica FP. Hospital tap water as a source of Stenotrophomonas maltophilia infection. Clin Infect Dis 2008;46(9):1485–7. https://doi.org/10.1086/587180

[12] Singhal L, Kaur P, Gautam V. Stenotrophomonas maltophilia: from trivial to grievous. Indian J Med Microbiol 2017;35(4):469–79. https://doi.org/10.4103/ijmm.IJMM_16_430

[13] Duan Z, Qin J, Liu Y, Li C, Ying C. Molecular epidemiology and risk factors of Stenotrophomonas maltophilia infections in a Chinese teaching hospital. BMC Microbiol 2020;20(1):294. https://doi.org/10.1186/s12866-020-01985-3

[14] Banar M, Sattari-Maraji A, Bayatinejad G, Ebrahimi E, Jabalameli L, Beigverdi R, et al. Global prevalence and antibiotic resistance in clinical isolates of Stenotrophomonas maltophilia: a systematic review and meta-analysis. Front Med 2023;10:1163439. https://doi.org/10.3389/fmed.2023.1163439

[15] AlFonaisan MK, Alghamdi SA, Alharbi AM, Aljohani SM, Alotaibi NM, Alshammari FA, et al. Temporal analysis of prevalence and antibiotic-resistance patterns in Stenotrophomonas maltophilia clinical isolates in a 19-year retrospective study. Sci Rep 2024;14(1):17853. https://doi.org/10.1038/s41598-024-65509-z

[16] Wang L, Zhang H, Li Y, Chen X, Zhao W, Liu J, et al. Molecular epidemiology, genetic diversity, antibiotic resistance and pathogenicity of Stenotrophomonas maltophilia complex from bacteremia patients in a tertiary hospital in China for nine years. Front Microbiol 2024;15:1424241. https://doi.org/10.3389/fmicb.2024.1424241

[17] Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 2015;6:893. https://doi.org/10.3389/fmicb.2015.00893

[18] Singh R, Kar M, Dubey A, Sahu C, Patel SS. Clinico-epidemiological analysis of Stenotrophomonas maltophilia bacteraemia, its associated risk factors and outcome in patients admitted at a tertiary care centre in Northern India: a retrospective cohort study. Natl J Lab Med 2024;13(3)–PO05. https://doi.org/10.7860/NJLM/2024/63439.2798

[19] Wang Y, Wang Y, Rong H, Guo Z, Xu J, Huang X. Risk factors of lower respiratory tract infection caused by Stenotrophomonas maltophilia: systematic review and meta-analysis. Front Public Health 2023;10:1035812. https://doi.org/10.3389/fpubh.2022.1035812

[20] Wang N, Tang C, Wang L. Risk factors for acquired Stenotrophomonas maltophilia pneumonia in intensive care unit: a systematic review and meta-analysis. Front Med 2022;8:808391. https://doi.org/10.3389/fmed.2021.808391

[21] Cruz-Córdova A, et al. Molecular epidemiology, antibiotic resistance, and virulence traits of Stenotrophomonas maltophilia strains associated with an outbreak in a Mexican tertiary care hospital. Front Cell Infect Microbiol 2020;10:50. https://doi.org/10.3389/fcimb.2020.00050

[22] Yashar M, et al. Stenotrophomonas maltophilia outbreak originating from a pull-out faucet in a pediatric intensive care unit in Turkey: insights from clinical records and molecular typing. Am J Infect Control 2024;52(5):605–10. https://doi.org/10.1016/j.ajic.2023.11.018

[23] Kazak E, et al. An evaluation of a Stenotrophomonas maltophilia outbreak due to commercial arterial blood gas collection kit. Antimicrob Resist Infect Control 2024;13(1):97. https://doi.org/10.1186/s13756-024-01410-8

[24] Matheu MB, Rice N, Singson K, St John B, Lindsay H, Burnett K, et al. Stenotrophomonas maltophilia outbreak associated with sink drains in an intensive care unit. Open Forum Infect Dis 2022;9(Suppl 2). https://doi.org/10.1093/ofid/ofac492.1053

[25] Guyot A, Turton JF, Garner D. Outbreak of Stenotrophomonas maltophilia on an intensive care unit. J Hosp Infect 2013;85(4):303–7. https://doi.org/10.1016/j.jhin.2013.09.007

[26] Khan S, Deida AV, Langerman S, Hunter JC, Halpin A, Kent A, et al. Stenotrophomonas maltophilia bloodstream infection outbreak in an acute care hospital–Alameda County, California, 2022–2023. Antimicrob Steward Healthc Epidemiol 2024;4(S1)–S123. https://doi.org/10.1017/ash.2024.280

[27] Sommer M, et al. Unveiling the structure, function and dynamics of StmPr1 in Stenotrophomonas maltophilia virulence. Sci Rep 2025;15:1–15. https://doi.org/10.1038/s41598-025-06177-5

[28] Mikhailovich V, Heydarov R, Zimenkov D, Chebotar I.Stenotrophomonas maltophilia virulence: a current view.Front Microbiol 2024;15:1385631. https://doi.org/10.3389/fmicb.2024.1385631

[29] Bhaumik R, Aungkur NZ, Anderson GG. A guide to Stenotrophomonas maltophilia virulence capabilities, as we currently understand them. Front Cell Infect Microbiol 2023;13:1322853. https://doi.org/10.3389/fcimb.2023.1322853

[30] Isom CM, Fort B, Anderson GG. Evaluating metabolic pathways and biofilm formation in Stenotrophomonas maltophilia. J Bacteriol 2022;204(7). https://doi.org/10.1128/JB.00398-21

[31] Li K, et al. Stenotrophomonas maltophilia complex: insights into evolutionary relationships, global distribution and pathogenicity. Front Cell Infect Microbiol 2023;13:1325379. https://doi.org/10.3389/fcimb.2023.1325379

[32] Brooke JS. Advances in the microbiology of Stenotrophomonas maltophilia. Clin Microbiol Rev 2021;34(3). https://doi.org/10.1128/CMR.00030-19

[33] Bhaumik R, Beard A, Harrigan O, Ramos-Hegazy L, Mattoo S, Anderson GG. Role of SMF-1 and cbl pili in Stenotrophomonas maltophilia biofilm formation. Biofilm 2025;9:100253. https://doi.org/10.1016/j.bioflm.2025.100253

[34] Rajeev R, et al. First report of Stenotrophomonas maltophilia from canine dermatological infections: unravelling its antimicrobial resistance, biofilm formation, and virulence traits. Antibiotics 2025;14(7):639. https://doi.org/10.3390/antibiotics14070639

[35] Sánchez MB. Antibiotic resistance in the opportunistic pathogen Stenotrophomonas maltophilia. Front Microbiol 2015;6:658. https://doi.org/10.3389/fmicb.2015.00658

[36] Ba X, et al. Old drugs to treat resistant bugs: methicillin-resistant Staphylococcus aureus isolates with mecC are susceptible to a combination of penicillin and clavulanic acid. Antimicrob Agents Chemother 2015;59(12):7396–404. https://doi.org/10.1128/AAC.01469-15

[37] Ibrahem K, et al. An in vitro investigation of the potential synergistic effect of 3-hydrazinoquinoxaline-2-thiol and thymoquinone against methicillin-resistant Staphylococcus aureus (MRSA). J Pure Appl Microbiol 2024;18(4):2837–49. https://doi.org/10.22207/JPAM.18.4.55

[38] Elfadil A, Ibrahem K, Abdullah H, Mokhtar JA, Al-Rabia MW, Mohammed HA. Synergistic activity of 3-hydrazinoquinoxaline-2-thiol in combination with penicillin against MRSA. Infect Drug Resist 2024;17:355–64. https://doi.org/10.2147/IDR.S448843

[39] Sánchez MB, Hernández A, Martinez J. Stenotrophomonas maltophilia drug resistance. Future Microbiol 2009;4(6):655–60. https://doi.org/10.2217/fmb.09.45

[40] Hu RM, Huang KJ, Wu LT, Hsiao YJ, Yang TC. Induction of L1 and L2 β-lactamases of Stenotrophomonas maltophilia. Antimicrob Agents Chemother 2008;52(3):1198–200. https://doi.org/10.1128/AAC.00682-07

[41] Al-Khafajy SQS, ALMuhana ASA, AL-sham JAB. PCR detection of genes encoded antibiotic resistance in Stenotrophomonas maltophilia isolated from clinical infections. Int J Health Sci (Qassim) 2022;6:3319–29. https://doi.org/10.53730/ijhs.v6nS8.12841

[42] Gil-Gil T, Martínez JL. Fosfomycin resistance evolutionary pathways of Stenotrophomonas maltophilia in different growing conditions. Int J Mol Sci 2022;23(3):1132. https://doi.org/10.3390/ijms23031132

[43] Zhao S, Yang L, Liu H, Gao F. Stenotrophomonas maltophilia in a university hospital of traditional Chinese medicine: molecular epidemiology and antimicrobial resistance. J Hosp Infect 2017;96(3):286–9. https://doi.org/10.1016/j.jhin.2017.04.001

[44] Crossman LC, Gould VC, Dow JM, Vernikos GS, Okazaki A, Sebaihia M, et al. The complete genome, comparative and functional analysis of Stenotrophomonas maltophilia reveals an organism heavily shielded by drug resistance determinants. Genome Biol 2008;9(4). https://doi.org/10.1186/gb-2008-9-4-r74

[45] Alonso A, Martínez JL. Multiple antibiotic resistance in Stenotrophomonas maltophilia. Antimicrob Agents Chemother 1997;41(5):1140–2. https://doi.org/10.1128/AAC.41.5.1140

[46] Yinsai O, Deeudom M, Duangsonk K. Genotypic diversity, antibiotic resistance, and virulence phenotypes of Stenotrophomonas maltophilia clinical isolates from a Thai university hospital setting. Antibiotics 2023;12(2):410. https://doi.org/10.3390/antibiotics12020410

[47] Ochoa-Sánchez LE, Martínez JL, Gil-Gil T. Evolution of resistance against ciprofloxacin, tobramycin, and trimethoprim/sulfamethoxazole in the environmental opportunistic pathogen Stenotrophomonas maltophilia. Antibiotics 2024;13(4):330. https://doi.org/10.3390/antibiotics13040330

[48] Youenou B, et al. Comparative genomics of environmental and clinical Stenotrophomonas maltophilia strains with different antibiotic resistance profiles. Genome Biol Evol 2015;7(9):2484–505. https://doi.org/10.1093/gbe/evv161

[49] Boncompagni SR, Riccobono E, Cusi MG, Di Pilato V, Rossolini GM. Evidence of dissemination of a clc-type integrative and conjugative element to Stenotrophomonas maltophilia, mediating acquisition of sul1 and other resistance determinants. Antimicrob Agents Chemother 2025;69(2). https://doi.org/10.1128/aac.01554-24

[50] Gil-Gil T, Martínez JL, Blanco P. Mechanisms of antimicrobial resistance in Stenotrophomonas maltophilia: a review of current knowledge. Expert Rev Anti Infect Ther 2020;18(4):335–47. https://doi.org/10.1080/14787210.2020.1730178

[51] Nicodemo AC, Paez JG. Antimicrobial therapy for Stenotrophomonas maltophilia infections. Eur J Clin Microbiol Infect Dis 2007;26(4):229–37. https://doi.org/10.1007/s10096-007-0279-3

[52] Mojica MF, Bonomo RA, Van Duin D. Treatment approaches for severe Stenotrophomonas maltophilia infections. Curr Opin Infect Dis 2023;36(6):512–20. https://doi.org/10.1097/QCO.0000000000000975

[53] Maraolo AE, Licciardi F, Gentile I, Saracino A, Belati A, Bavaro DF. Stenotrophomonas maltophilia infections: a systematic review and meta-analysis of comparative efficacy of available treatments, with critical assessment of novel therapeutic options. Antibiotics 2023;12(5):910. https://doi.org/10.3390/antibiotics12050910

[54] Gibb J, Wong DW. Antimicrobial treatment strategies for Stenotrophomonas maltophilia: a focus on novel therapies. Antibiotics 2021;10(10):1226. https://doi.org/10.3390/antibiotics10101226

[55] Bostanghadiri N, et al. Global mapping of antibiotic resistance rates among clinical isolates of Stenotrophomonas maltophilia: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob 2024;23(1):56. https://doi.org/10.1186/s12941-024-00685-4

[56] Kullar R, Wenzler E, Alexander J, Goldstein EJC. Overcoming Stenotrophomonas maltophilia resistance for a more rational therapeutic approach. Open Forum Infect Dis 2022;9(5). https://doi.org/10.1093/ofid/ofac095

[57] Barrasa H, et al. Optimizing antibiotic therapy for Stenotrophomonas maltophilia infections in critically ill patients: a pharmacokinetic/pharmacodynamic approach. Antibiotics 2024;13(6):553. https://doi.org/10.3390/antibiotics13060553

[58] Falagas ME, Valkimadi PE, Huang YT, Matthaiou DK, Hsueh PR. Therapeutic options for Stenotrophomonas maltophilia infections beyond co-trimoxazole: a systematic review. J Antimicrob Chemother 2008;62(5):889–94. https://doi.org/10.1093/jac/dkn301

[59] Méndez-Sotelo BJ, et al. In vitro activity of ceftazidime/avibactam, cefiderocol, meropenem/vaborbactam and imipenem/relebactam against clinical strains of the Stenotrophomonas maltophilia complex. PLoS One 2024;19(4). https://doi.org/10.1371/journal.pone.0298577

[60] Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. Antimicrob Agents Chemother 2013;57(11):5548–58. https://doi.org/10.1128/AAC.01288-13

[61] Xiao M, et al. Antimicrobial activity of omadacycline in vitro against bacteria isolated from 2014 to 2017 in China, a multi-center study. BMC Microbiol 2020;20(1):231. https://doi.org/10.1186/s12866-020-02019-8

[62] Junco SJ, Bowman MC, Turner RB. Clinical outcomes of Stenotrophomonas maltophilia infection treated with trimethoprim/sulfamethoxazole, minocycline, or fluoroquinolone monotherapy. Int J Antimicrob Agents 2021;58(2):106367. https://doi.org/10.1016/j.ijantimicag.2021.106367

[63] Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. Clin Microbiol Infect 2008;14(9):816–27. https://doi.org/10.1111/j.1469-0691.2008.02061.x

[64] Martínez-Servat S, et al. Heterogeneous colistin-resistance phenotypes coexisting in Stenotrophomonas maltophilia isolates influence colistin susceptibility testing. Front Microbiol 2018;9:2758. https://doi.org/10.3389/fmicb.2018.02871

[65] Zhou J, Chen Y, Tabibi S, Alba L, Garber E, Saiman L. Antimicrobial susceptibility and synergy studies of Burkholderia cepacia complex isolated from patients with cystic fibrosis. Antimicrob Agents Chemother 2007;51(3):1085–8. https://doi.org/10.1128/AAC.00954-06

[66] Ciacci N, et al. In vitro synergism of colistin and N-acetylcysteine against Stenotrophomonas maltophilia. Antibiotics 2019;8(3):101. https://doi.org/10.3390/antibiotics8030101

[67] Paškevičius Š, Gleba Y, Ražanskienė A. Stenocins: novel modular bacteriocins from opportunistic pathogen Stenotrophomonas maltophilia. J Biotechnol 2022;351:9–12. https://doi.org/10.1016/j.jbiotec.2022.04.006

[68] Paprocka P, et al. Bactericidal activity of ceragenin in combination with ceftazidime, levofloxacin, co-trimoxazole, and colistin against the opportunistic pathogen Stenotrophomonas maltophilia. Pathogens 2022;11(6):621. https://doi.org/10.3390/pathogens11060621

[69] Gordon NC, Wareham DW. Antimicrobial activity of the green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) against clinical isolates of Stenotrophomonas maltophilia. Int J Antimicrob Agents 2010;36(2):129–31. https://doi.org/10.1016/j.ijantimicag.2010.03.025

[70] Zhang Y, et al. Antibacterial activity of essential oils against Stenotrophomonas maltophilia and the effect of citral on cell membrane. LWT 2020;117:108667. https://doi.org/10.1016/j.lwt.2019.108667

[71] Esposito A, et al. Antibacterial and antivirulence activity of glucocorticoid PYED-1 against Stenotrophomonas maltophilia. Antibiotics 2020;9(3):105. https://doi.org/10.3390/antibiotics9030105

[72] Sanders MI, et al. Antibacterial activity of the novel drug gepotidacin against Stenotrophomonas maltophilia: an in vitro and in vivo study. Antibiotics 2022;11(2):192. https://doi.org/10.3390/antibiotics11020192

[73] Nguyen THT, et al. Plant secondary metabolites on efflux-mediated antibiotic resistant Stenotrophomonas maltophilia: potential of herbal-derived efflux pump inhibitors. Antibiotics 2023;12(2):421. https://doi.org/10.3390/antibiotics12020421

[74] Yuan YG, Wang YH, Liu WL, Guo LX, Li XJ, Liu Y. Anti-Stenotrophomonas maltophilia mechanism of rose essential oil: a metabolomic study. Food Bioprocess Technol 2024;17(9):2693–705. https://doi.org/10.1007/s11947-023-03285-w

[75] Sreenithya KH, Jade D, Harrison MA, Sugumar S. Identification of natural inhibitor against L1 β-lactamase present in Stenotrophomonas maltophilia. J Mol Model 2022;28(11):341. https://doi.org/10.1007/s00894-022-05336-z

[76] Jdeed G, et al. StM171, a Stenotrophomonas maltophilia bacteriophage that affects sensitivity to antibiotics in host bacteria and their biofilm formation. Viruses 2023;15(12):2455. https://doi.org/10.3390/v15122455

[77] Monsibais AN, et al. Enhanced suppression of Stenotrophomonas maltophilia by a three-phage cocktail: genomic insights and kinetic profiling. Antimicrob Agents Chemother 2025;69(3). https://doi.org/10.1128/aac.01162-24

[78] Cheng P, et al. Characterization of the novel cross-genus phage vB_SmaS_QH3 and evaluation of its antibacterial efficacy against

Stenotrophomonas maltophilia. Front Microbiol 2025;16:1570665. https://doi.org/10.3389/fmicb.2025.1570665
[79] Hagh Ranjbar H, Hosseini-Abari A, Ghasemi SM, Hafezi Birgani Z. Antibacterial activity of epsilon-poly-L-lysine produced by Stenotrophomonas maltophilia HS4 and Paenibacillus polymyxa HS5, alone and in combination with bacteriophages. Microbiology 2023;169(7):001363. https://doi.org/10.1099/mic.0.001363
[80] Cheng P, et al. Characterization and antimicrobial activity of a novel lytic phage vB_SmaS_QH16 against Stenotrophomonas maltophilia: in vitro, in vivo, and biofilm studies. Front Cell Infect Microbiol 2025;15:1610857. https://doi.org/10.3389/fcimb.2025.1610857
[81] McCutcheon JG, Lin A, Dennis JJ. Isolation and characterization of the novel bacteriophage axl3 against Stenotrophomonas maltophilia. Int J Mol Sci 2020;21(17):6338. https://doi.org/10.3390/ijms21176338
[82] Han K, et al. Potential application of a newly isolated phage BUCT609 infecting Stenotrophomonas maltophilia. Front Microbiol 2022;13:1001237. https://doi.org/10.3389/fmicb.2022.1001237
[83] Li Y, et al. Efficacy in Galleria mellonella larvae and application potential assessment of a new bacteriophage BUCT700 extensively lysing Stenotrophomonas maltophilia. Microbiol Spectr 2023;11(1). https://doi.org/10.1128/spectrum.e04030-22
[84] Han P, et al. Characterization of the bacteriophage BUCT603 and therapeutic potential evaluation against drug-resistant Stenotrophomonas maltophilia in a mouse model. Front Microbiol 2022;13:906961. https://doi.org/10.3389/fmicb.2022.906961
[85] Peters DL, McCutcheon JG, Dennis JJ. Characterization of novel broad-host-range bacteriophage DLP3 specific to Stenotrophomonas maltophilia as a potential therapeutic agent. Front Microbiol 2020;11:1358. https://doi.org/10.3389/fmicb.2020.01358
[86] Li F, et al. Isolation and characterization of the novel bacteriophage vB_SmaS_BUCT626 against Stenotrophomonas maltophilia. Virus Genes 2022;58(5):458–66. https://doi.org/10.1007/s11262-022-01917-5

Related articles

1. Biosurfactant derived from probiotic Lactobacillus acidophilus exhibits broad-spectrum antibiofilm activity and inhibits the quorum sensing-regulated virulence

Mohd Adnan et al., Biomol Biomed, 2023

2. Molecular characterization and genotype of multi-drug resistant *Staphylococcus epidermidis* in nasal carriage of young population, Mahasarakham, Thailand

Peechanika Chopjitt et al., Biomol Biomed, 2024