

# From Opportunist to Menace: Rising Antimicrobial Resistance in *Serratia Marcescens*

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**Abstract:** Initially identified as a low-virulence opportunistic bacterium, *Serratia marcescens* has emerged as a significant pathogen, particularly in high-risk settings. Increasing reports of multidrug-resistant (MDR) and carbapenem-resistant (CR) isolates emphasise its role in healthcare-associated infections. Outbreaks have been documented, often linked to invasive devices, contaminated solutions, and lapses in infection prevention and control (IPC). While data from Southeast Asia remains limited, evidence suggests an upward trend. This narrative review summarises developments in *S.marcescens* resistance and therapeutic options. A PRISMA-informed search was conducted in ScienceDirect, PubMed and Google Scholar for English-language articles published between 2019 and 2025. Eligible studies included original research, surveillance reports, and case reports. Data were synthesised qualitatively. Published literature describes a global rise in resistant isolates. *S.marcescens* demonstrates intrinsic resistance to colistin, ampicillin, and first-generation cephalosporins, while also harbouring inducible AmpC  $\beta$ -lactamase. Acquisition of extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemases further limits therapeutic options. Ceftazidime-avibactam (CZA) alone or in combination with aztreonam demonstrates efficacy against KPC-producing strains and metallo- $\beta$ -lactamase producers. Cefiderocol, despite limited availability, has shown promising activity. In conclusion, the rising resistance of *S.marcescens* underscores the need for strengthened microbiological surveillance and antimicrobial stewardship. Future research should prioritise local resistance mechanisms and the optimisation of therapeutic strategies.

## 1 INTRODUCTION

*Serratia marcescens* is a Gram-negative opportunistic pathogen widely distributed in environmental and healthcare settings, with increasing recognition as a cause of healthcare-associated infections, particularly among critically ill and immunocompromised patients (Tavares-Carreón et al., 2023). It has been implicated in a wide spectrum of infections, including bloodstream infections, pneumonia, urinary tract infections, and outbreaks in intensive care units, often associated with invasive procedures and contaminated medical equipment. Its ability to persist in hospital environments and evade disinfection contributes to its role in nosocomial transmission and outbreak potential (Xia et al., 2025).

In recent years, *S. marcescens* has gained attention due to the increasing emergence of multidrug-resistant (MDR) and carbapenem-resistant (CR) strains, posing significant therapeutic challenges. This organism exhibits a complex resistome driven by intrinsic, acquired, and adaptive mechanisms, including inducible AmpC  $\beta$ -lactamase and the acquisition of extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemases. The global rise of resistance,

including plasmid-mediated dissemination of resistance genes, further complicates infection control and limits effective treatment options (Cosimato et al., 2024). Despite these advances, therapeutic decision-making remains highly challenging due to the discordance between in vitro susceptibility, underlying resistance mechanisms, and limited clinical outcome data.

Although several reviews have addressed resistance mechanisms or treatment strategies of *S. marcescens*, most are either focused on molecular aspects of resistance or limited to case-based therapeutic evidence. Moreover, available systematic reviews are often limited by small sample sizes and rely heavily on case reports and case series, reflecting the scarcity of robust clinical data. There remains a lack of integrative reviews that simultaneously synthesise recent epidemiological trends, resistance mechanisms, and emerging therapeutic options within a clinically relevant framework, particularly in low- and middle-income countries, including Southeast Asia. Therefore, this narrative review aims to provide an updated and comprehensive synthesis of antimicrobial resistance patterns and therapeutic strategies for *S. marcescens*, with a focus on recent developments (2019–2025). This review

uniquely integrates epidemiology, resistance mechanisms, and therapeutic strategies within a clinically actionable framework, with particular attention to evidence gaps in low- and middle-income settings.

## 2 METHODS

This narrative review was conducted using a PRISMA-informed approach. A comprehensive literature search was performed in PubMed, ScienceDirect, and Google Scholar for studies published between 2019 and 2025.

Search terms included combinations of the following keywords: “*Serratia marcescens*”, “antimicrobial resistance”, “multidrug-resistant”, “carbapenem-resistant”, “ESBL”, and “treatment”, using Boolean operators (AND/OR) as appropriate. Reference lists of relevant articles were also screened to identify additional studies. Titles and abstracts were screened independently by two reviewers. Full-text articles were assessed based on predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion.

Inclusion criteria were:

- (1) studies involving *S. marcescens* with a focus on antimicrobial resistance mechanisms or treatment;
- (2) original research articles, surveillance studies, or review articles; and
- (3) publications in peer-reviewed journals between 2019 and 2025.

Exclusion criteria were:

- (1) non-English publications;
- (2) case reports lacking adequate microbiological or therapeutic data;
- (3) studies involving non-clinical isolates or other *Serratia* species; and
- (4) conference abstracts without accessible full texts.

The review process followed key principles of the PRISMA 2020 statement, although no formal meta-analysis was performed. Data extraction was performed independently by two reviewers using a standardized form. Extracted data included study design, geographic region, resistance mechanisms, and reported therapeutic approaches. Findings were synthesised qualitatively, focusing on trends in antimicrobial resistance and emerging treatment options.

## 3 RESULT

### Global Epidemiology of *Serratia marcescens*

Epidemiological data on *S. marcescens* in Indonesia remain limited, with most available evidence derived from studies in Asia and other low- and middle-income settings. Globally, *S. marcescens* is increasingly recognized as a healthcare-associated pathogen, particularly among critically ill and immunocompromised patients, and is implicated in a wide spectrum of infections, including bloodstream, respiratory, and urinary tract infections (Boldeanu et al., 2025).

A recent study conducted in Iraqi intensive care units uncovered a strikingly high incidence of MDR *S. marcescens*. Out of 101 clinical isolates examined through biochemical and molecular analyses, 71 were confirmed to exhibit multidrug resistance. The strains showed widespread resistance to  $\beta$ -lactam antibiotics, with the blaCTX-M and blaSHV genes detected in every isolate. In addition, blaCMY and blaTEM were present in roughly 95% and 89% of isolates, respectively. Alarmingly, up to 90% of samples carried carbapenemase genes, underscoring the extensive resistance load and highlighting the growing clinical threat posed by MDR *S. marcescens* in Iraqi ICU environments (AL-Kadmy et al., 2025).

According to a genomic study conducted by Chen et al. (2025), the global population structure of *S. marcescens* exhibits remarkable genetic diversity and widespread antimicrobial resistance. By analysing 1,464 genome sequences collected from 33 countries, eleven predominant antimicrobial resistance genes (ARGs) were detected among *S. marcescens* isolates. The *sde* gene was the most abundant, appearing 2,985 times, and is known to encode an efflux pump system that plays a pivotal role in facilitating multidrug resistance. Other commonly identified genes included *aadY*, *smfY*, *tet*, *blaSRT*, and *blaSST-1*, which collectively mediate resistance against aminoglycosides, tetracyclines, and  $\beta$ -lactam antibiotics. Furthermore, the genes *armA* and *rmtC*, which confer high-level resistance to aminoglycosides, and the plasmid-mediated fosfomycin resistance gene *fosA7.2* were identified for the first time in this species, underscoring ongoing genetic adaptation and horizontal acquisition of novel resistance determinants.

Several key variants regarding carbapenemase genes were identified: blaSME (n=33), blaKPC (n=40), blaNDM-1 (n=21), blaVIM (n=5), blaOXA-48 (n=3), blaIMP-1 (n=1), and blaGES-49 (n=1). Interestingly, no single isolate carried more than one carbapenemase gene, suggesting that carbapenem

resistance in *S. marcescens* generally arises from a single predominant enzymatic mechanism. From a geographical perspective, blaKPC and blaNDM-1 displayed the broadest global distribution, particularly in the United States, China, and South Asian regions such as Bangladesh. Meanwhile, blaSME appeared largely restricted to North America, whereas blaOXA-48 and blaVIM occurred infrequently and within more confined geographic ranges (Chen et al., 2025).

Zhu et al. (2025) reported a difference in antimicrobial susceptibility profiles between MDR and non-MDR *Serratia marcescens* isolates from 242 hospitalized patients. In general, non-MDR strains displayed broad susceptibility, with rates exceeding 78% for nearly all tested antimicrobials, whereas MDR isolates exhibited a sharp decline in responsiveness, with susceptibility ranging only from 11.8% to 36.3%. Among the aminoglycoside class, amikacin retained the greatest activity, remaining effective in 68.2% of MDR isolates and 96.2% of non-MDR strains. In contrast, tobramycin and gentamicin were notably less active against MDR isolates, with respective susceptibility rates of 11.8% and 23.5%, although both agents preserved more than 78% activity in non-MDR isolates. This marked disparity between MDR and non-MDR isolates highlights the clinical importance of early resistance detection, as delayed appropriate therapy may significantly impact outcomes.

For  $\beta$ -lactam agents such as ceftriaxone, ceftazidime, and cefepime, efficacy against MDR isolates was markedly diminished, with only 5.9–22.7% remaining susceptible, while non-MDR strains maintained high sensitivity (94.3–97.9%). Likewise, aztreonam and piperacillin/tazobactam exhibited limited activity in the MDR group (both showing 31.8% resistance) but preserved over 90% susceptibility among non-MDR isolates. Imipenem demonstrated moderate effectiveness in MDR isolates (36.3% susceptible) and full susceptibility in non-MDR ones. Interestingly, sulfamethoxazole showed relatively strong efficacy even in MDR isolates (68.2% susceptible) and excellent activity in non-MDR counterparts (98.1%). On the other hand, fluoroquinolones (including ciprofloxacin and levofloxacin) were largely ineffective against MDR strains, with susceptibility rates of 17.6% and 18.2%, respectively, though they remained highly active against non-MDR isolates, exceeding 92% susceptibility (Zhu et al., 2025).

Based on the genomic analysis carried out by Overmeyer et al. (2023) in Cape Town, South Africa, whole-genome sequencing of twenty-one carbapenem-resistant *Serratia marcescens* (CRSM) isolates, along with four carbapenem-susceptible counterparts, revealed a remarkably diverse resistance gene repertoire. A total of twenty-four unique

antimicrobial resistance determinants were identified, with all isolates harbouring at least two genes and seventeen carrying three or more. This genetic diversity was highly consistent with the phenotypic resistance profiles, reinforcing the molecular basis of the observed multidrug resistance pattern.

The blaOXA-48-like carbapenemase gene was the dominant resistance determinant, found in 86% (18/21) of CRSM isolates, underscoring its major contribution to carbapenem resistance in this setting. Furthermore, shared plasmid profiles were observed in eleven isolates, supporting the likelihood of horizontal gene transfer as a major mechanism for resistance spread. Beyond resistance, the study also detected several candidate virulence genes and SNPs potentially linked to enhanced pathogenicity, though their biological significance remains to be clarified through functional assays (Overmeyer et al., 2023).

A longitudinal surveillance study carried out at the University Hospital “San Giovanni di Dio e Ruggi d’Aragona” in Salerno, Italy, from 2015 to 2022, analyzed 396 clinical isolates of *Serratia marcescens* obtained from diverse patient samples. Throughout this eight-year observation period, the research documented notable shifts in antimicrobial resistance patterns across multiple antibiotic groups. Initially, resistance to penicillin derivatives such as amoxicillin/clavulanic acid, was remarkably high at 89.1%, showing a consistent increase in the following years. In contrast, ceftazidime/avibactam remained the most effective agent with the lowest resistance levels, followed by amikacin and trimethoprim/sulfamethoxazole. Within the cephalosporin group, resistance rates were 20.7% for ceftazidime and 25.3% for cefotaxime, while cefepime demonstrated the most favourable result, with resistance dropping to 8% by 2022 (Cosimato et al., 2024).

Carbapenem resistance, initially minimal at 4.2% for meropenem, varied over time, peaking at 7.5% in 2020. Meanwhile, fluoroquinolone resistance—most notably against ciprofloxacin increase dramatically from 2.1% in 2015 to 39.7% in 2021, reflecting an increasing trend likely associated with extensive antibiotic exposure. In contrast, resistance to trimethoprim/sulfamethoxazole remained relatively constant, averaging around 5.7% (Cosimato et al., 2024).

Over a five-year period, a retrospective analysis carried out at Sohar Hospital in northern Oman evaluated 257 *Serratia* isolates obtained between 2017 and 2021 to determine resistance trends. The study demonstrated notably high resistance rates among  $\beta$ -lactam antibiotics, with ampicillin (99.5%), cefuroxime (99.1%), amoxicillin-clavulanic acid (98.6%), and ceftazidime (48%) emerging as the least effective agents. In contrast, carbapenems and several

non- $\beta$ -lactam antibiotics exhibited strong antibacterial performance. Only a small proportion of isolates were resistant to imipenem (8.1%) and meropenem (7.6%). Similarly, high susceptibility levels were retained for trimethoprim-sulfamethoxazole (93.5%), ciprofloxacin (92.4%), gentamicin (90.7%), and amikacin (92.5%). Strikingly, all tested isolates were completely sensitive to tigecycline (100%), emphasizing its continued reliability as a treatment option for *Serratia* infections (Sannathimmappa et al., 2024).

## Global Outbreak

During an outbreak of multidrug-resistant (MDR) *Serratia marcescens* at a tertiary public university hospital in Cuiabá, Mato Grosso, Brazil, ten isolates were collected from patients in the ICU as well as medical and surgical wards between September and December 2018. Of the affected individuals, six were men (60%), and four were women (40%), with an average age of  $58.8 \pm 18.6$  years. Samples were taken from tracheal aspirate, catheter tip, rectal swab, pleural fluid, abdominal secretions, synovial fluid, and blood. The outbreak was associated with a high mortality rate of 40% (4 out of 10 patients). Laboratory testing showed that all isolates were uniformly resistant to a broad range of antibiotics, including penicillins (piperacillin/tazobactam), cephalosporins (cefepime), carbapenems (imipenem, meropenem, and ertapenem), fluoroquinolones (ciprofloxacin), and polymyxins (polymyxin B), highlighting the extensive multidrug-resistant profile of the outbreak strains (Cruz et al., 2021).

Meanwhile, in a 28-bed neonatal intensive care unit outbreak, environmental sampling revealed that sinks in multiple ICU wings were likely sources of contamination. Prompt infection control interventions, including strict hand hygiene, isolation of infected or colonized infants, intensified environmental disinfection with sodium hypochlorite, replacement and sealing of contaminated sinks, modification of milk preparation and incubator humidification procedures, and reinforcement of eye-care protocols effectively contained the outbreak and prevented further spread (Ismail et al., 2025).

In a cardiothoracic surgery unit, an outbreak of *S. marcescens* was reported, involving 23 out of 47 postoperative patients who all tested positive via blood cultures. Treatment for the affected patients was guided by antimicrobial susceptibility results, with cefepime administered accordingly. The hospital's infection control team conducted a thorough investigation, which included active surveillance, staff interviews, and environmental sampling across 225

sites, such as blood cultures, medical equipment, therapeutic solutions, and antiseptics. Contaminated pre-prepared flushing syringes were identified as the probable source of the outbreak. Enhanced surveillance and strict review of hand hygiene, infusion preparation, device usage, and cleaning practices were implemented in the unit to prevent further spread (Papagianni et al., 2025).

The increasing frequency of outbreaks and the observed variability in antimicrobial susceptibility highlight the importance of understanding the underlying resistance mechanisms that drive these clinical patterns.

## Antibiotic Resistance Mechanism

The antimicrobial resistance phenotype of *S. marcescens* is not driven by a single mechanism, but rather by the interaction of multiple intrinsic, chromosomal, and acquired factors.

### Efflux pumps

Efflux pumps are transmembrane protein complexes that are able to expel toxic substances from the bacterial cytoplasm into the extracellular space. These systems can detect and transport a wide array of harmful molecules, such as detergents, fatty acids, heavy metals, bile salts, dyes, and various antibiotics. As a result, they play a major role in shaping the intrinsic resistance profiles of many bacterial species. Furthermore, mutations in efflux pump genes may alter their substrate range, thereby conferring acquired resistance to additional antimicrobial agents. Six main efflux pump families have been identified. The ATP-binding cassette (ABC) transporters utilize energy generated through ATP hydrolysis to drive substrate export. In contrast, the major facilitator superfamily (MFS), small multidrug resistance (SMR), multidrug and toxic compound extrusion (MATE), resistance-nodulation-cell division (RND) superfamily, and proteobacterial antimicrobial compound efflux (PACE) families function as secondary active transporters that rely on electrochemical ion gradients to power substrate movement across the membrane (Tavares-Carreón et al., 2023).

One important mechanism contributing to antimicrobial resistance in *Serratia marcescens* is the activity of multidrug efflux pumps, particularly those belonging to the resistance-nodulation-division (RND) family. Among these, the SdeAB and SdeXY systems have been well characterized and are known to mediate energy-dependent extrusion of a wide range of antimicrobial agents. The SdeAB efflux pump has been shown to confer decreased susceptibility to fluoroquinolones, chloramphenicol, and other structurally diverse compounds, with overexpression

of the *sdeB* gene observed in a substantial proportion of clinical isolates exhibiting reduced fluoroquinolone susceptibility (Kumar and Worobec, 2005). Similarly, the SdeXY system, the first RND-type efflux pump identified in *S. marcescens*, contributes to intrinsic multidrug resistance by actively exporting agents such as tetracyclines, fluoroquinolones, and disinfectants (Chen et al., 2003). These efflux systems function in conjunction with outer membrane proteins (e.g., TolC homologues) and are driven by the proton motive force, enabling broad substrate specificity and reduced intracellular antibiotic accumulation. Collectively, the overexpression and regulation of these efflux pumps play a significant role in both intrinsic and acquired resistance phenotypes in *S. marcescens*, particularly under antibiotic or biocide selective pressure (Toba et al., 2019).

#### Porin alteration

Alterations in outer membrane porins play a critical role in mediating antimicrobial resistance in *S. marcescens* by reducing antibiotic influx. Experimental and clinical studies have demonstrated that decreased expression or loss of major porins (including OmpF- and OmpC-like proteins) significantly lowers outer membrane permeability, thereby limiting the influx of  $\beta$ -lactams and other hydrophilic agents. In porin-deficient mutants of *S. marcescens*, permeability to cephalosporins such as cephaloridine was reduced by approximately 30- to 200-fold, highlighting the substantial barrier effect imposed by porin loss (Espana et al., 2003). Importantly, this mechanism rarely acts in isolation. Instead, porin downregulation synergizes with chromosomal AmpC  $\beta$ -lactamase overproduction, a combination that has been shown to confer resistance even to carbapenems such as meropenem in *S. marcescens* isolates. This reduced permeability significantly limits the effectiveness of  $\beta$ -lactam antibiotics, particularly when combined with enzymatic resistance mechanisms (Tavares-Carreón et al., 2023).

#### Modification of lipopolysaccharide

As a Gram-negative bacterium, *S. marcescens* possesses an outer membrane that limits permeability, creating a robust barrier that restricts the passive diffusion of hydrophobic antibiotics, including cationic antimicrobial peptides (CAPs). These CAPs typically bind to lipopolysaccharides (LPS) in the outer membrane, disrupting the  $Mg^{2+}$ -mediated cross-bridges between negatively charged LPS molecules. This disruption compromises the structural integrity of the cell envelope, ultimately causing bacterial death. The LPS itself consists of three main components: lipid A, a core oligosaccharide, and the O-antigen. Chemical alterations in either the lipid A or the core

oligosaccharide, often through the addition of positively charged groups, have been linked to *S. marcescens* resistance against CAPs. In addition, *S. marcescens* exhibits intrinsic resistance to polymyxins (including colistin), largely due to structural characteristics of its outer membrane lipopolysaccharide (LPS), which reduce binding affinity of the drug and limit its bactericidal activity (Tavares-Carreón et al., 2023).

#### Chromosomal resistance enzymes

In *S. marcescens*, as in other members of the *Enterobacteriales* family,  $\beta$ -lactam resistance is primarily driven by the production of penicilloyl-serine transferases, more commonly known as  $\beta$ -lactamases. These enzymes include AmpC-type cephalosporinases, extended-spectrum  $\beta$ -lactamases (ESBLs) that can inactivate third-generation cephalosporins and aztreonam, as well as various carbapenemases. A major determinant of *S. marcescens* intrinsic resistance is the presence of chromosomally encoded  $\beta$ -lactamases, particularly the inducible AmpC enzyme, which confers resistance to a broad range of  $\beta$ -lactam antibiotics. AmpC  $\beta$ -lactamase in *S. marcescens* is typically expressed at low basal levels but can be strongly induced or derepressed through mutations in regulatory genes, leading to high-level resistance to penicillins, first- and second-generation cephalosporins, and reduced susceptibility to extended-spectrum cephalosporins. The combination of inducible AmpC production and intrinsic permeability barriers forms a baseline resistance phenotype that can be further enhanced by additional mechanisms such as porin loss and efflux pump overexpression. Importantly, derepressed AmpC expression has been associated with treatment failure during  $\beta$ -lactam therapy, particularly when using third-generation cephalosporins, underscoring its clinical relevance in antimicrobial selection and stewardship. (Jacoby, 2009; Tamma et al., 2021).

One notable chromosomally encoded carbapenemase is the *S. marcescens* enzyme (SME), which possesses the ability to hydrolyze a broad range of  $\beta$ -lactams including penicillins, cephalosporins, aztreonam, and imipenem thereby conferring significant resistance (Tavares-Carreón et al., 2023).

#### Horizontal transfer of $\beta$ -lactamase genes

The emergence of multidrug-resistant *S. marcescens* is increasingly driven by the acquisition of plasmid-mediated  $\beta$ -lactamases, including extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemases. Among these, enzymes such as KPC, NDM, VIM, and OXA-type carbapenemases have been identified in clinical isolates of *S. marcescens*, often conferring high-level resistance to carbapenems and other  $\beta$ -

lactams. Outbreak investigations have reported clonal spread of KPC-producing *S. marcescens* associated with plasmid carriage, highlighting the role of mobile resistance determinants in nosocomial transmission (Cruz et al., 2021; Overmeyer et al., 2023).

Horizontal gene transfer plays a central role in the dissemination of these resistance determinants. Plasmids, transposons, and integrons enable the capture and transfer of  $\beta$ -lactamase genes between *S. marcescens* and other members of the Enterobacterales, contributing to the accumulation of multidrug resistance. In particular, class 1 integrons have been implicated in the co-transfer of multiple resistance genes, allowing simultaneous resistance to  $\beta$ -lactams, aminoglycosides, and fluoroquinolones. Clinical reports have also documented the emergence of metallo- $\beta$ -lactamase-producing *S. marcescens* through acquisition of *bla*NDM genes, often carried on transferable plasmids, further limiting therapeutic options (Ruan et al., 2025; Taha et al., 2023). These findings underscore that, beyond intrinsic and chromosomal mechanisms, the adaptive success of *S. marcescens* is strongly linked to its capacity for horizontal gene acquisition, which accelerates the spread of resistance within and between healthcare environments. This capacity for horizontal gene transfer positions *S. marcescens* as both a recipient and reservoir of resistance genes within hospital microbial ecosystems.

Taken together, antimicrobial resistance in *S. marcescens* is driven by a multifaceted interplay between intrinsic, chromosomal, and acquired mechanisms that collectively shape its multidrug-resistant phenotype. Intrinsically, the organism exhibits reduced susceptibility to several antibiotic classes through baseline expression of AmpC  $\beta$ -lactamase and low outer membrane permeability, while adaptive responses such as efflux pump overexpression and porin downregulation further decrease intracellular antibiotic accumulation. These intrinsic and chromosomal features are frequently compounded by the acquisition of mobile genetic elements carrying resistance determinants, including ESBLs and carbapenemases, which can be rapidly disseminated via horizontal gene transfer. Recent genomic analyses have demonstrated that *S. marcescens* harbours a diverse resistome enriched with plasmid-associated  $\beta$ -lactamase genes and integron structures, facilitating interspecies gene exchange within Enterobacterales and promoting the emergence of high-risk clones in healthcare settings (Sandner-Miranda et al., 2018; Cosimato et al., 2024). Importantly, the convergence of these mechanism, particularly AmpC overexpression combined with decreased permeability and acquired carbapenemases,

can result in high-level resistance even to last-line agents, significantly limiting therapeutic options and complicating clinical management. This integrated resistance architecture underscores the remarkable adaptability of *S. marcescens* under antimicrobial pressure and highlights the need for comprehensive surveillance strategies that consider both phenotypic resistance patterns and underlying genetic determinants. From a clinical perspective, this layered resistance architecture explains the frequent discordance between in vitro susceptibility and clinical response, particularly in severe infections. It also underscores why monotherapy may fail despite apparent susceptibility, reinforcing the need for mechanism-informed therapeutic strategies.

### Conventional Therapy

For susceptible *S. marcescens* infections, conventional antimicrobial therapy remains the mainstay of treatment. Broad-spectrum  $\beta$ -lactam antibiotics, including cefepime and piperacillin-tazobactam, are commonly used because they are stable against AmpC  $\beta$ -lactamases when appropriately dosed. However, caution is warranted when using third-generation cephalosporins due to the risk of AmpC derepression and subsequent treatment failure, even when initial susceptibility is reported. Cefepime, in particular, has been shown to retain activity against AmpC-producing Enterobacterales and is often preferred in settings where inducible resistance is a concern (Tamma et al., 2021).

Carbapenems, such as meropenem and imipenem, are generally reserved for severe infections or cases involving resistant isolates. These agents provide reliable activity against many  $\beta$ -lactamase-producing organisms and are frequently employed in critically ill patients. However, their widespread use has been associated with the emergence of carbapenem-resistant strains, emphasizing the importance of judicious prescribing (Papp-Wallace et al., 2011).

Aminoglycosides, particularly amikacin, remain valuable adjuncts in the treatment of *S. marcescens* infections. Several surveillance studies have demonstrated relatively preserved susceptibility to amikacin compared with other aminoglycosides, making it a useful option for combination therapy in severe infections. Its bactericidal activity and synergy with  $\beta$ -lactams further support its role in clinical practice (Ramirez & Tolmasky, 2017).

Fluoroquinolones and trimethoprim-sulfamethoxazole may be considered in selected cases, particularly for less severe infections or when oral therapy is appropriate. However, increasing resistance rates to fluoroquinolones have been reported globally, necessitating susceptibility-guided use. Overall, conventional therapy remains effective for susceptible

isolates but requires careful selection to minimize resistance development.

#### Advance Therapy

The treatment of MDR and CR *S. marcescens* has become increasingly challenging, necessitating the use of newer  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations and alternative agents. Ceftazidime–avibactam (CZA) has emerged as a key therapeutic option, particularly for infections caused by KPC-producing strains. Avibactam effectively inhibits class A and some class D  $\beta$ -lactamases, restoring the activity of ceftazidime against resistant organisms (Shields et al., 2017).

A clinical case report from Cape Town, South Africa, described the management of a 17-month-old female burn patient (46% total body surface area) who developed a persistent infection caused by CR *S. marcescens* during an extended hospital stay. Empirical antimicrobial therapy failed to control the infection, prompting susceptibility testing that confirmed sensitivity to CZA. Following institutional and regulatory approval, CZA was administered at a dosage of 50 mg/kg every eight hours, in combination with tigecycline, amikacin, and colistin. After seven days of therapy, the patient showed significant clinical improvement and was transferred from the ICU to the general ward. The patient subsequently completed an additional four-week course of therapy, achieving full microbiological clearance and complete clinical recovery (Tootla et al., 2021).

Importantly, resistance to CZA has already been reported, particularly in isolates with complex  $\beta$ -lactamase profiles, highlighting the need for cautious and targeted use. CZA alone is not effective against metallo- $\beta$ -lactamase (MBL)-producing isolates, such as those harbouring NDM or VIM enzymes. In these cases, combination therapy with aztreonam has demonstrated promising results. Aztreonam remains stable against MBL hydrolysis, while avibactam protects it from co-produced serine  $\beta$ -lactamases, making the combination a rational and increasingly utilized strategy for treating MBL-producing Enterobacterales (Falcone et al., 2020).

Researchers at the Microbiology Department, Medical Research Institute, Alexandria University, investigated to assess the synergistic efficacy of combining CZA with aztreonam (ATM) against carbapenem-resistant Enterobacterales. Synergistic activity between CZA and ATM was detected in 79 (98.75%) of *Klebsiella* and 19 (95%) of *E. coli* isolates, including all pan drug-resistant strains. The majority of isolates showing synergy were resistant to either or both agents when tested separately, underscoring the enhanced efficacy of the combined regimen against MBL-producing pathogens (Taha et al., 2023).

Researchers at the First Affiliated Hospital of Guangxi Medical University also investigated the synergistic efficacy of combining ceftazidime–avibactam with aztreonam against carbapenem-resistant Enterobacterales (CRE). A total of 87 unique clinical isolates were obtained from various specimen sources. All CRE isolates demonstrated complete resistance (100%) to most  $\beta$ -lactam antibiotics, notably cefazolin, ceftriaxone, piperacillin/tazobactam, ertapenem, and meropenem. Among isolates harbouring a single carbapenemase gene. The CZA–ATM combination produced synergistic effects in 95.4% (83/87) of all CRE isolates tested. This synergy was observed in 100% of isolates lacking detectable carbapenemase genes, 94.3% of blaNDM-positive strains, and 100% of isolates carrying blaNDM coexisting with blaKPC-2 or blaIMP-4 genes. These findings underscore the potent synergism of CZA and ATM against multidrug-resistant pathogens expressing diverse carbapenemase profiles (Ruan et al., 2025).

#### Cefiderocol

Cefiderocol, a siderophore cephalosporin, represents another important therapeutic advance. This agent utilizes bacterial iron transport systems to gain entry into the periplasmic space, thereby overcoming resistance mechanisms related to porin loss and efflux. In vitro studies have shown potent activity against a broad range of CR Gram-negative pathogens, including *S. marcescens*, although clinical data remain limited (Ito et al., 2018).

Large-scale surveillance analyses from the SIDERO-WT program evaluated the in vitro efficacy of cefiderocol against a diverse array of clinically significant Gram-negative pathogens. The findings consistently demonstrated potent antibacterial activity, with more than 99% of isolates exhibiting low cefiderocol MIC values. Among Enterobacterales species, including *Escherichia coli*, *Klebsiella spp.*, *Citrobacter spp.*, *Enterobacter spp.*, and *Serratia spp.*, the MIC<sub>90</sub> values ranged from 0.25 to 1  $\mu$ g/mL, underscoring cefiderocol's robust activity against a wide spectrum of Gram-negative organisms.

In the complementary SIDERO-CR program, carbapenem-resistant isolates collected from Europe, North America, South America, and the Asia-Pacific region were evaluated. The results demonstrated that cefiderocol maintained strong in vitro activity against a broad spectrum of carbapenemase-producing organisms, regardless of bacterial species or the molecular class of  $\beta$ -lactamase. Potent efficacy was observed against class A enzymes (KPC and GES), class B metallo- $\beta$ -lactamases (VIM, NDM, and IMP), and class D oxacillinases (OXA-23, -24/40, -48, and -58), with MIC<sub>90</sub> values ranging between 0.5 and 8  $\mu$ g/mL. These findings highlight cefiderocol's broad-

spectrum stability against diverse carbapenemase mechanisms across global clinical isolates (Yamano, 2019).

Despite these advances, treatment of MDR *S. marcescens* remains complex, often requiring individualized regimens based on resistance mechanisms and patient factors. The emergence of resistance even to novel agents highlights the need for continued surveillance and cautious use of these therapies.

#### Emerging Resistance and Future Perspectives

The rapid evolution of antimicrobial resistance in *S. marcescens* underscores the need for innovative therapeutic strategies and a more comprehensive approach to infection management. Increasing reports of resistance to novel agents, including CAZ, highlight the organism's ability to adapt under antimicrobial pressure and emphasize the importance of preserving the efficacy of new drugs (Wang et al., 2022).

Future treatment approaches are likely to rely more heavily on combination therapy, particularly for severe infections caused by MDR organisms. Combining agents with complementary mechanisms of action may enhance bacterial killing and reduce the likelihood of resistance emergence. Additionally, pharmacokinetic/pharmacodynamic (PK/PD)-guided dosing strategies are increasingly recognized as essential for optimizing therapeutic outcomes (Roberts et al., 2014).

Beyond antibiotic selection, effective management of *S. marcescens* infections requires a multidisciplinary approach that includes prompt source control, accurate microbiological diagnosis, and antimicrobial stewardship. Stewardship programs play a critical role in minimizing unnecessary antibiotic exposure, thereby reducing selective pressure and slowing the spread of resistance (Dyar et al., 2017).

Advances in molecular diagnostics and genomic surveillance are also expected to improve the identification of resistance mechanisms and guide targeted therapy. As our understanding of *S. marcescens* resistance continues to evolve, integrating microbiological, clinical, and epidemiological data will be essential for developing effective and sustainable treatment strategies. Future strategies should incorporate rapid molecular diagnostics to enable mechanism-based therapy, particularly in settings with high prevalence of carbapenemase-producing organisms.

## 4 CONCLUSIONS

*Serratia marcescens* has evolved into a clinically significant multidrug-resistant pathogen, particularly in healthcare settings where selective antimicrobial

pressure and invasive interventions are common. Its resistance profile is driven by a complex interplay of intrinsic, chromosomal, and horizontally acquired mechanisms, resulting in highly adaptable and often unpredictable phenotypes.

The increasing emergence of MDR and CR strains significantly limits conventional therapeutic options and necessitates the use of newer agents such as ceftazidime–avibactam, aztreonam-based combinations, and cefiderocol. However, clinical evidence supporting these therapies remains limited, and resistance to novel agents is already being reported.

Effective management of *S. marcescens* infections therefore requires an integrated approach that combines early microbiological diagnosis, mechanism-informed antimicrobial selection, and robust antimicrobial stewardship. Strengthening genomic surveillance and expanding clinical outcome data will be critical to guide future therapeutic strategies.

Ultimately, bridging the gap between microbiological understanding and clinical application will be essential to improve patient outcomes and contain the ongoing threat posed by this increasingly resilient pathogen.

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