Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 9
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

A Seven-Year Surveillance of Epidemiological Trends of *Serratia marcescens* with Different Infection Types in a Tertiary Hospital in China

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Abstract: Objective: To explore the trend of detection and antimicrobial resistance of Serratia marcescens with different infection types for 7 consecutive years, to provide a reference for future studies for the control of S. marcescens infections and a rational selection of antibiotics. Methods: S. marcescens isolates were collected from 2014 to 2020, and the trend of detection and antimicrobial resistance were analyzed according to different types of infection. Results: For 7 consecutive years, the data showed that patients with S. marcescens infections were mainly from the intensive care unit (ICU) (384 isolates, 40.98%), and the isolates recovered were mainly from sputum samples (743 isolates, 79.30%). The number of isolated strains increased every year, and the average rate of detection ranged from 0.60% to 0.80%. The detection rate of S. marcescens with hospital-acquired infections (HAI) showed a downward trend and that of S. marcescens with colonization showed an upward trend. The detection rate of multidrug-resistant S. marcescens fluctuated between 8.33%–16.89%. The resistance rate of S. marcescens to piperacillin was 17.0%–29.06% and the resistance rate to piperacillin tazobactam was 2.95%–13.13%. For cephalosporin antibiotics, the resistance rates of S. marcescens to cefuroxime and cefazolin were > 99% and the resistance rates to ceftazidime and cefepime were < 13%. The resistance rate of S. marcescens to aminoglycoside antibiotics, especially amikacin, was the lowest. The resistance rate of S. marcescens with community-acquired infections (CAI) to carbapenems was higher than that with HAI and colonization. Conclusion: The different infection types of S. marcescens have different detection and epidemic trends. In addition, resistance to carbapenems is different across the strains.

Keywords: Serratia marcescens; Infection; Carbapenems; Drug resistance

Online publication: Oct 16, 2025

1. Introduction

Serratia marcescens is gram-negative bacillus, belonging to the family Enterobacteriaceae. It is an opportunistic pathogen, common in aquatic animals, insects, and plants. In 1913, *S. marcescens* was discovered to be pathogenic, but its pathogenicity was underestimated. It was not until 1951, when the first nosocomial infection caused by *S. marcescens* occurred, that it was gradually paid attention to [1]. *S. marcescens* is associated with a wide spectrum of clinical diseases, including bloodstream infections, conjunctivitis, pneumonia, urinary tract infections, meningitis with or without intracerebral abscess formation, and surgical site infection [2, 3]. Previous epidemiological data has shown that infections caused by *S. marcescens* were not common. According to the hospital infection surveillance system by the European Centre for Disease Prevention and Control, *S. marcescens* ranked sixth in causing pneumonia, tenth in causing bloodstream infections, and sixth in causing urinary tract infections [4]. Overall, the incidence rate is low and has not attracted much attention. However, *S. marcescens* infections result in a higher mortality rate; for example, bloodstream infection mortality is > 40% and necrotizing fasciitis mortality is as high as > 60% [5, 6]. In addition, *S. marcescens* can often adhere to medical equipment, implanted catheters, and the hands of medical personnel, leading to a series of outbreaks [7, 8]. Studies have shown that *S. marcescens* was responsible for five out of 39 pathogen-induced nosocomial infection outbreaks, most of which occurred in the neonatal intensive care unit [8]. After *S. marcescens* infection, the colonization may last for 1–7 months, making outbreak control difficult. For example, the *S. marcescens* outbreak in Switzerland lasted for 12 months in 2016 [9]. In addition, an 11-month *S. marcescens* epidemic was reported in Turkey in the same year [10]. The frequent outbreaks constantly remind us to pay attention to the severe infection situation of *S. marcescens* [11].

In recent years, *S. marcescens* resistance to several drugs has attracted increased attention. It can develop resistance to β-lactamase antibiotics by producing inducible β-lactamase and extended-spectrum β-lactamase (ESBL). β-lactam antibiotics are one of the most common antibiotics used in the treatment of bacterial infections, making *S. marcescens* infections difficult to treat [12]. Some studies have discovered drug sensitivity for other antibacterial drugs, such as aminoglycosides [13,14]. Furthermore, the drug resistance rate of *S. marcescens* to carbapenems has gradually increased in recent years, which poses challenges to the prevention, control, and clinical treatment of hospital infections [15]. Carbapenems are the last line of defense for the treatment of gram-negative bacterial infections; their effectiveness in treatment is worth paying attention to. The purpose of this study is to understand the changing trend in the detection and drug resistance of *S. marcescens* through the analysis of surveillance data for 7 consecutive years. In addition, the different infection types and the similarities and differences in drug resistance rates to carbapenems were analyzed to further guide the diagnosis, treatment, prevention, and control of *S. marcescens*.

2. Materials and methods

2.1. Source of the strain

From January 1, 2014, to December 31, 2020, *S. marcescens* isolated from clinical specimens in the First Affiliated Hospital with Nanjing Medical University, Nanjing were retrospectively collected from a real-time surveillance system for nosocomial infections. Strains repeated in the same part of the same patient were eliminated, and the specimens were confirmed to be qualified. Ethical approval for this retrospective study was obtained from the local ethics committee of the First Affiliated Hospital with Nanjing Medical University (2022-SR-034). The study was conducted in accordance with relevant guidelines and regulations.

2.2. Definition

Based on infection type, *S. marcescens* was divided into community-acquired infection (CAI) sources, hospital-acquired infection (HAI) sources, and colonization. CAI was defined as infection occurring within 48 hours after admission, HAI was defined as infection occurring after 48 hours, and colonization was defined as the absence of any clinical manifestations at the site of specimen origin, except for contamination. Multidrug-resistant *S. marcescens* was defined as simultaneous resistance to three or more classes of antibiotics in clinical use [16]. The detection trend of *S. marcescens*, the changing trend of composition ratio of different infection types, the detection trend of multidrug-resistant *S. marcescens*, and the antimicrobial resistance trend of *S. marcescens* were studied.

2.3. Identification of bacteria and drug sensitivity test

The Vitek-2 Compact automated bacterial identification instrument (Biomeerier, France) was used for bacterial identification. Sensitivity test was performed using the disk diffusion method (Oxide Company). The control strain (Clinical Laboratory Center of National Health and Family Planning Commission) was *S. marcescens* (ATCC14756). The sensitivity results were interpreted according to the 2017 Clinical and Laboratory Standards Institute Standards [17].

2.4. Statistic analysis

SPSS software version 21.0 (SPSS Inc., Chicago, IL) was used for data description and analysis. The χ^2 test was used to analyze the difference in the serotype composition ratio of *S. marcescens* infection. All statistical tests were two-sided, and a P value of < 0.05 was considered to be statistically significant.

3. Results

3.1. Distribution of S. marcescens sources

The specimens were obtained from ICU, surgery department, and geriatrics department, accounting for > 85%. The main sources of the specimens were sputum, secretions, and urine, accounting for almost 90% in total (**Table 1**).

Table 1. Annual average detection rates of *S. marcescens* (%)

	Number	Proportion
Departments		
Internal medicine	97	10.35%
Surgery	260	27.75%
Gynecology	2	0.21%
Pediatric	10	1.07%
Recovery	24	2.56%
ICU	384	40.98%
Geriatric	153	16.33%
Emergency	7	0.75%
Specimens		
Tissue	4	0.43%

Table 1 (Continued)

	Number	Proportion
Urine	43	4.59%
Blood	35	3.74%
Hydrothorax and ascites	9	0.96%
Sputum	743	79.30%
Secreta	48	5.12%
Fester	24	2.56%
Irrigating solution	17	1.81%
Bile	9	0.96%
Other	5	0.53%

3.2. Average annual detection rate of S. marcescens

The number of *S. marcescens* detected and the total number of pathogens isolated showed an increasing trend each year for 7 consecutive years. A total of 937 strains were detected, and the average annual percentage of *S. marcescens* ranged from 0.60% to 0.80%, with the lowest rate of 0.60% in 2019 and the highest rate of 0.80% in 2015 (**Table 2**).

Table 2. Annual average detection ratio of *S. marcescens* (%)

	Number of strains	Number of pathogenic strains isolated	Proportion
2014	110	15507	0.71%
2015	121	15191	0.80%
2016	120	15724	0.76%
2017	123	17759	0.69%
2018	140	20650	0.68%
2019	148	24784	0.60%
2020	175	23419	0.75%

3.3. Trend of annual composition ratio of S. marcescens infection type

For 7 consecutive years, the proportion of *S. marcescens* from CAI was stable and fluctuated at approximately 30%. The proportion of *S. marcescens* from colonization increased from 13.79% to 44.57%. The proportion of *S. marcescens* from HAI decreased from 51.72% to 22.29%. The results are illustrated in **Figure 1**.

3.4. Trend of detection rates of multidrug-resistant S. marcescens

The detection rates of multidrug-resistant *S. marcescens* fluctuated between 8.33% and 16.89% for 7 consecutive years, with the highest at 16.89% in 2019 and the lowest at 8.33% in 2016. The results are illustrated in **Figure 2**.

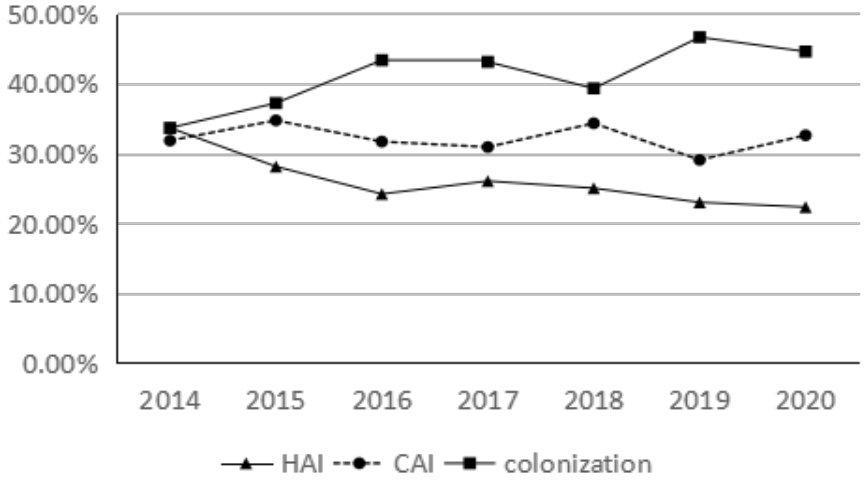

Figure 1. The proportion of different *Serratia marcescens* infection types by year

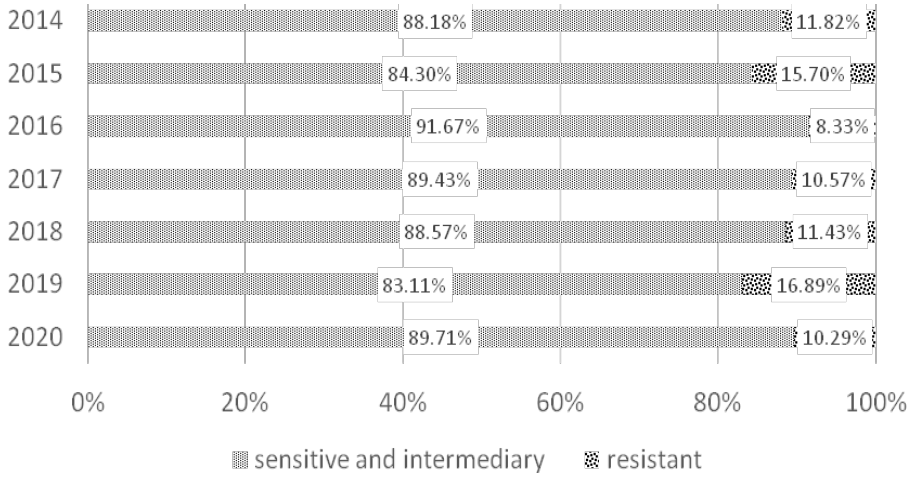

Figure 2. Annual detection rates of multidrug-resistant *Serratia marcescens*

3.5. Antibiotic resistance of S. marcescens

For 7 consecutive years, *S. marcescens* showed some degree of drug resistance to piperacillin and piperacillin tazobactam. Piperacillin had the highest drug resistance rate in 2017 (35.45%), and the resistance rate in other years ranged from 17% to 29.06%. The resistance rate of *S. marcescens* to piperacillin tazobactam ranged from 2.95% to 13.13%. For cephalosporin antibacterial drugs, the drug resistance rates of *S. marcescens* to cefuroxime and cefazolin were above 99%, showing strong drug resistance, while the drug resistance rates to ceftazidime and cefepime were below 13%, showing a certain degree of sensitivity. Furthermore, *S. marcescens* showed resistance to other β-lactam antibiotics, such as aztreonam and quinolone antibiotics, with drug resistance rates ranging from 9.77% to 30.86%. After 2018, the resistance of *S. marcescens* to meropenem and imipenem showed an increasing trend to some extent. Amikacin had the strongest antibacterial activity, with a drug resistance rate of 0% in 2019 and 2020 (**Table 3**).

Table 3. Results of antibacterial resistance of *S. marcescens*

	2014	2015	2016	2017	2018	2019	2020
Piperacillin	18.0	15.9	26.5	35.5	29.1	21.8	21.2
Piperacillin tazobactam	11.9	6.5	6.1	2.9	7.6	13.1	7.3
Cefoperazone-sulbactam	20.0	14.5	13.4	17.9	22.8	14.0	25.4
Ceftazidime	9.0	5.8	5.7	3.7	5.9	7.6	2.5
Cefepime	10.2	9.3	6.9	4.8	8.5	12.0	4.0
Cefuroxime	100.0	99.3	100.0	100.0	100.0	100.0	100.0
Cefazolin	100.0	99.4	100.0	100.0	100.0	100.0	100.0
Ceftriaxone	22.6	18.8	27.4	37.7	31.9	26.54	22.5
Aztreonam	19.3	15.0	25.2	25.5	25.3	18.9	16.8
Imipenem	13.1	11.9	8.7	8.7	21.6	16.4	16.1
Meropenem	8.2	10.3	5.7	6.7	19.4	14.5	12.8
Tobramycin	12.3	7.1	4.1	4.9	15.9	12.4	2.5
Gentamicin	18.3	13.5	7.4	7.0	15.7	7.5	2.5
Amikacin	7.6	1.7	1.7	1.4	0.3	0	0
Levofloxacin	9.8	10.8	23.1	27.0	14.6	18.7	20.6
Ciprofloxacin	17.9	16.0	21.6	30.9	25.6	21.2	24.2

3.6. Drug resistance rate of S. marcescens to carbapenems for different infection types

The results of the story show that the drug resistance rate of *S. marcescens* from CAI was significantly higher than that from HAI and colonization ($P < 0.001$ for imipenem and $P = 0.002$ for meropenem). The drug resistance rate of *S. marcescens* from CAI to imipenem and meropenem showed an increasing trend from 2018 to 2020 (**Table 4**).

Table 4. Drug resistance rates of *S. marcescens* from different sources to carbapenems

	Types of infection	2014	2015	2016	2017	2018	2019	2020	χ^2	*P*
Imipenem	CA	15.38	23.64	10.94	17.07	41.79	30.59	41.09	38.42	< 0.001
	HA	14.35	14.74	5.36	4.71	13.41	19.23	1.74		
	Colonization	2.27	3.64	9.17	4.60	5.56	6.92	5.41		
Meropenem	CA	16.22	19.64	7.94	14.29	37.41	27.91	35.66	31.17	0.002
	HA	7.32	14.74	5.36	4.30	11.76	16.22	1.71		
	Colonization	8.00	1.82	4.55	2.15	5.30	6.17	1.96		

4. Discussion

The data show that the main concentration of *S. marcescens* infections is in ICU (40.98%), which is similar to the results of Bo-Huang and Şimşek [18, 19]. However, the percentage in this study is higher than that in their studies. For sample types of *S. marcescens*, this study showed that sputum (79.30%) was the dominant sample type,

which is consistent with the trend observed by Bo-Huang [18]. However, the proportion was markedly higher in this study than the latter. Analysis of sputum specimens showed that almost half were colonized (data not shown). In addition, previous studies have confirmed that *S. marcescens* is easily colonized in the respiratory and urinary tracts in adult patients [20, 21]. The total number of detected strains and the total number of isolated pathogens increased every year. The highest number of detected strains was 175 in 2020, but the total proportion was < 1%, which is slightly lower than the results reported by Wang in China [22]. This finding indicates that the prevalence of *S. marcescens* in some regions of China is low. As far as it is understood, this study is the first to classify detected *S. marcescens* strains into HA, CA, and colonization bacteria according to infection type, to further analyze the possible patterns and sources. The results of this study showed that HAI *S. marcescens* remarkably decreased from 51.2% to 22.3% during the 7 years. CAI *S. marcescens* infections accounted for approximately 30% infections, while colonization with *S. marcescens* showed an increasing trend, which may indicate that HAI *S. marcescens* infections reduced to a certain extent. However, due to the widespread presence of *S. marcescens* in nature and the hospital environment, more patients acquired *S. marcescens* from the environment but did not develop a disease. In addition, in immunocompromised, young, and elderly populations, colonization bacteria have considerable invasive power to cause infection [23]. Therefore, the surveillance and analysis of the trend of an *S. marcescens* epidemic should be actively performed, along with reasonable interpretation of data. Furthermore, active screening can be conducted for high-risk groups, such as newborns, and prevention and control measures should be taken in advance and at the earliest [21].

The results showed that the detection rate of multidrug-resistant *S. marcescens* reached 16.89% in 2019. In addition to the innate resistance to tetracycline and polymyxins, the production of β-lactamases, including ESBL and cephalosporin enzyme (AmpC enzyme), are the main reasons for resistance of *S. marcescens* to β-lactamases [24]. In this study, piperacillin had the highest drug resistance rate (35.45%) in 2017, which ranged from 17% to 29.06% in other years. However, the drug resistance rate of piperacillin and tazobactam was remarkably lower than that of piperacillin, ranging from 2.95% to 13.13%, which was lower than the results of 19.6% [19]. As a β-lactamase inhibitor, tazobactam reduced the drug resistance rate of related *S. marcescens* strains to a certain extent, but the change of the membrane pore protein and active pumping system were mechanisms contributing to a certain degree of resistance to the drugs. For cephalosporin antibacterial drugs, *S. marcescens* resistance rates, first to cephalosporin and second to cephalosporin, were >99%, closely related to the innate drug resistance [25]. The drug resistance rate of ceftriaxone of the third-generation cephalosporins (18.8%–37.7%) was higher than that of ceftazidime (3.7%–9.0%), which was similar to that of the fourth-generation cephalosporins.

The quinolone antibacterial drugs levofloxacin and ciprofloxacin had an increasing trend in resistance for 7 consecutive years, and the highest resistance rate was approximately 30% in 2017. This is similar to the results by Gonzalez but markedly higher than the results by Şimşek [18, 23]. All samples from the latter study were obtained from blood, indicating that the drug resistance rates of *S. marcescens* is different from different sample sources. Multiple results have shown that aminoglycosides such as amikacin had strong antibacterial activity against *S. marcescens*, which is consistent with the results of this study [13,19]. No drug-resistant strains were detected in 2019 and 2020. However, previous studies suggested that aminoglycoside resistance was high, which may be related to the frequency of the use of aminoglycoside antibacterial drugs [26]. The use of aminoglycoside was limited in recent years in China and the drug resistance decreased. In addition, the side effects with aminoglycoside use, such as ototoxicity and nephrotoxicity affect its application in clinical practice [14].

Carbapenems are a class of atypical β-lactam antibacterial drugs that are characterized by strong antibacterial

activity and stability to ESBLs and AmpC enzymes. According to a report released by the China Antimicrobial Resistance Surveillance System in 2016, drug resistance rates of *Serratia* (dominated by *S. marmaris*, 87.5%) to carbapenems such as meropenem and ertapenem increased from 0.5% and 1.6% in 2005 to 7% and 6.8% in 2014. It ranks first in the growth rate of common antimicrobial drug resistance, and the situation is not optimistic [27]. In addition, the results of the study showed that the drug resistance rate of *S. marmaris* to meropenem and imipenem increased considerably after 2017–2018. The drug resistance rate of > 10% was similar to the results by Şimşek but markedly higher than those by GM Gonzalez, which showed a drug resistance rate of < 5% [19, 23]. Zhang showed that the drug resistance rate of *S. marcescens* to imipenem was as high as 25.6%, which completely demonstrates the severity of carbapenem-resistant *S. marcescens* in some regions of China [28]. The main mechanism of *S. marcescens* resistance to carbapenems is the production of carbapenase [20, 29]. Furthermore, *S. marcescens* is naturally resistant to polymyxin, which makes treatment difficult [14]. To further explore the trend of carbapenem-resistant *S. marcescens*, this study classified *S. marcescens* into three sources, HAI, CAI, and colonization, and compared the drug resistance rates to carbapenem antibiotics. It was observed that the drug resistance rate of CAI-based *S. marcescens* to carbapenem was remarkably higher than that of HAI and colonization. One possible reason for this could be that patients with CAI may have been referred to this facility from other hospitals. Therefore, the patient could have acquired the infection at another hospital. As a regional medical center, it is common for this institution to accept transferred patients. Therefore, from the perspective of other hospitals, the patient is likely to have a HAI. In addition, the patient may have used several antibacterial drugs at the previous medical institution, which may have exacerbated drug resistance. Although the drug resistance rate of *S. marcescens* is low, it can result in an infection under favorable conditions. In addition, the drug resistance rates of *S. marcescens* to imipenem and meropenem showed a steep downward trend from 19.23% to 1.74% and 16.22% to 1.71% in 2019 and 2020, respectively. It is believed that the strict prevention and control measures due to the COVID-19 pandemic may have played a role in the decreasing rates.

5. Limitations

Despite the promising findings, this study has some limitations. First, this study was a single-center study; therefore, most research categories were not represented. Second, this study was also a traditional epidemiological study, without in-depth analysis of drug resistance of *S. marcescens* by molecular biological methods. Further in-depth analysis is required to explore this topic in the future.

6. Conclusions

The prevalence of *S. marcescens* in Jiangsu Province, China was not high but showed an increasing trend every year. The proportion of multidrug-resistant *S. marcescens* was high and resistance to some β-lactam antibiotics, especially carbapenems, showing an increasing trend and sensitivity with different *S. marcescens* infection types to carbapenems, was markedly different. Different infection types of *S. marcescens* have different detection and epidemic trends. In addition to routine surveillance, the infection type of clinical isolated specimens should be differentiated, and community acquisition and colonization should be focused on to provide added insights into the prevention and treatment of *S. marcescens* infections.

Funding

Hospital Management Innovation Program of Jiangsu Hospital Association in 2021 (Project No.: JSYGY-3-2021-511)

Disclosure statement

The authors declare no conflict of interest.

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