

## Review

### History and Presence of *Serratia marcescens*

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#### Abstract

*Serratia marcescens* is an important member of the order *Enterobacterales*, even though it was initially considered to be slightly virulent. Today it is an indisputable fact that *Serratia* is an important opportunistic pathogen responsible for a wide range of nosocomial infections. The main risk group is immunocompromised patients, both adults and newborns, and patients after different medical interventions such as bronchoscopy, central venous catheterization, urinal catheters, surgical drainage, tracheostomy, and mechanical ventilation. This species is documented as a causative agent of a variety of infections with different clinical presentations – bloodstream infections, respiratory and urinary tract infections, wound infections, and skin and soft tissue infections. In addition, *S. marcescens* is of high significance as an opportunistic pathogen due to its antibiotic resistance, which makes the treatment difficult. The types and the epidemiology of *S. marcescens* infections are presented and discussed in detail in this review.

**Keywords:** *Serratia marcescens*, opportunistic pathogen, nosocomial infections, epidemiology

#### Резюме

*Serratia marcescens* е значим представител на разред *Enterobacterales*, макар и първоначално да е смятан за слабо вирулентен. Днес е неспорим факт, че *Serratia* е изключително важен опортюнист, отговорен за редица нозокомиални инфекции. Главната рискова група са имунокомпрометирани пациенти - възрастни и новородени, пациенти след различни интервенции като бронхоскопия, централна венозна катетеризация, уринални катетри, дренажи, трахеостомия, механична вентилация. Бактериалният вид е доказан като агент, причиняващ най-разнообразни инфекции с различна клинична манифестация – бактериемия и сепсис, респираторни и уринарни инфекции, раневи, кожни инфекции и мекотъканни инфекции. Значимостта на *S. marcescens* е голяма и заради антибиотичната ѝ резистентност, която безспорно затруднява лечението. Видовете и епидемиологията на *S. marcescens* – асоциираните инфекции са представени и разгледани детайлно в това ревю.

#### Introduction

*Serratia marcescens* is a Gram-negative, facultative anaerobic bacteria, classified in the *Yersiniaceae* family, order *Enterobacterales* (Adeolu *et al.*, 2016). Specific characteristics of the genus *Serratia* are its ability to produce lipase, gelatinase, and DNase enzymes. A unique feature of *S. marcescens* is serrawettin production, a substance that acts as an adhesin, mediating the colonization of different surfaces. Extracellular enzymes such as nucleases, proteases, and hemolysin are also involved in the pathogenesis of species-associated diseases (Cooney *et al.*, 2014).

In 1819 in Padua, the Italian pharmacist Bartolomeo Bizio described an unusual red coloration

of polenta (an Italian dish made from cornmeal) after a relatively hot and humid summer. He succeeded in isolating the causative agent and named it *Serratia marcescens* in 1823. Before this discovery, the observed phenomenon has been called “bloody polenta” and people believed in its diabolical origin (Merlino, 1924).

The first reported clinical case of *S. marcescens*-associated infection was published in 1913 by Woodward and Clarke (Woodward and Clarke, 1913). The authors described a patient, complaining of chronic, persistent cough for 3 years, suspicious of tuberculosis, because of the foul-smelling and red color expectorations, defined as pseudohe-

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mophtysis (appearance of red-colored sputum in the absence of erythrocytes), which is a specific clinical manifestation of *S. marcescens* infection, attributed to the ability of some strains to produce a red pigment called prodigiosin (Grimont and Grimont, 2006). Apart from pseudohemoptysis but because of the same unusual pigmentation, *S. marcescens* was known to be associated with the “red diaper syndrome” (Waisman and Stone, 1958). The physiological role of prodigiosin remains unclear, but antibacterial, antimycotic, and antiprotozoal properties are suspected (Su *et al.*, 2016). Most clinical strains do not produce prodigiosin, which leads to the conclusion that it is not directly related to the pathogenesis of the diseases associated with this bacterial species. After years of debate about the clinical significance of such phenomena, today it is clear that *S. marcescens* is a typical opportunist, responsible for a variety of infectious syndromes, mainly in risk groups – immunocompromised individuals, newborns, patients after catheterization, etc.

### **Epidemiology**

Although ubiquitous microorganisms, the members of the genus *Serratia* are not considered part of the human normal intestinal flora (Stankovic *et al.*, 2014). *S. marcescens* can also be found in the hospital environment, contaminating different objects. Among the reported contaminated sources are medications, saline solutions and disinfectants, staff hands (Donnenberg, 2010), inhalers, drugs for inhalation therapy, air conditioning units, shaving brushes used before surgery (Géry *et al.*, 2021), tap water from pressure-monitoring equipment, containers for measuring and collecting urine, urinals, bronchoscopes, laryngoscopes, reusable rectal balloons, electrodes for electrocardiograms, vitrectomy devices, glass syringes, physiological solutions, heparinized saline, nonmedicated liquid soap, liquid soap dispenser, tap water used to take oral medications, betamethasone injections, propofol (Cilli *et al.*, 2018), fentanyl (Chiang *et al.*, 2013), breast milk.

Among the most important and socially significant causative agents of nosocomial infections is the so-called ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*) from order *Enterobacterales*, where *S. marcescens* also belongs. These pathogens have high levels of acquired multidrug resistance, often because of incorrect and uncontrolled use of antibiotics. The major role of *S. marcescens* as an opportunistic pathogen, main-

ly associated with hospital-acquired infections, has been recognized in the past several decades. Prolonged hospitalization, placement of intravenous, intraperitoneal, and urinary catheters, intubation, bronchoscopy, mechanical ventilation, a) other invasive procedures are major risk factors for *Serratia*-associated infections (Tóth *et al.*, 2020; Mendes and Casado, 2022). *S. marcescens* is documented as a causative agent of a variety of infections with different clinical presentation – mainly respiratory and urinary tract infections (UTIs), bloodstream infections, wound infections, as well as skin and soft tissue infections (Tan *et al.*, 2020; Martin *et al.*, 2022).

### **Urinary tract infections**

*S. marcescens* is one of the ten most common bacterial pathogens in patients with UTIs according to *HAI-Net* (Healthcare-Associated Infections Surveillance Network) of the European Centre for Disease Prevention and Control (ECDC, 2018). Most infections are exogenous, usually after catheterization, which is considered the main risk factor. Diabetes mellitus, urinary tract obstruction, and kidney failure are also identified as important predisposing factors (Golemi-Kotra *et al.*, 2008). Symptoms include dysuria, pyuria, fever, frequent urination, or pain upon urination. Recent analysis from Bulgaria shows that *S. marcescens* is commonly isolated from hospitalized patients with UTI (BulSTAR, 2018). A large, retrospective study of nosocomial multidrug-resistant *S. marcescens* UTIs in 329 patients showed that 16 cases were fatal due to secondary bloodstream infection. Most of the patients were elderly, had a prolonged hospital stay, or had an indwelling urinary catheter (Liu *et al.*, 2004). Another study claims that patients with *S. marcescens* UTIs are fourfold more likely to have poor outcomes than the general population of patients with UTIs (Krieger *et al.*, 1983).

### **Respiratory tract infections**

*S. marcescens* was the sixth most common cause of hospital-acquired pneumonia in Europe in 2016 based on data from ECDC (ECDC, 2018). These infections are usually preceded by invasive procedures such as bronchoscopy, intubation, mechanical ventilation, tracheostomy (Tan *et al.*, 2020) and are often diagnosed in patients with underlying chronic pulmonary diseases (ECDC, 2010). In addition to the classical symptoms of pneumonia like fever, dyspnea, chest pain, and productive cough, pseudohemoptysis due to the production of the red prodigiosin pigment can be demonstrated in

some cases (Zarogoulidis *et al.*, 2011; Ranjan *et al.*, 2018).

There are registered outbreaks of *S. marcescens* in COVID-19 ICUs, causing mainly ventilator-associated pneumonia, bacteremia, and sepsis even in immunocompetent hosts (Kewan *et al.*, 2020; Walters *et al.*, 2022). *S. marcescens* is recognized as a relatively common microorganism in patients with cystic fibrosis. In a research from 2016, 9.4% (29/318) of the patients gave sputum positive for *S. marcescens* (Lata *et al.*, 2016). Joyutpal Das *et al.* (2015) reported a case of *S. marcescens* community-acquired pneumonia in a patient with a cough as the only symptom. On the chest X-ray, multiple bilateral rounded opacities and mediastinal lymphadenopathy were demonstrated, which was suspicious for tuberculosis or disseminated malignancy. The sputum and bronchial washing samples grew only *S. marcescens*. Therefore, despite the few reported cases of *Serratia* granuloma, it should not be excluded.

### **Bloodstream infections**

According to ECDC reports from 2017, *Serratia* spp. accounts for 3% of all bloodstream infections in Europe. Patients with *Serratia*-associated sepsis demonstrate fever, chills, shock, and respiratory distress. The representatives of this genus are among the tenth most frequently isolated organisms associated with bacteremia in the ICUs. (ECDC, 2010) It is known that bacteremia usually develops after primary urinary or respiratory infection. Some researchers successfully identified the source of these infections. A sepsis outbreak was reported in 2018 in three patients after chest surgery and usage of contaminated propofol (Géry *et al.*, 2018), an outbreak in Taiwan was also reported due to contaminated intravenous pain control fluids (Cilli *et al.*, 2018), contaminated heparin-saline solutions used to flush deep venous catheters or peripheral trocars (Liu *et al.*, 2011). Cases of bloodstream infections were documented in nineteen patients receiving contaminated bags of parenteral nutrition and nine of these patients died (Gupta *et al.*, 2014). An outbreak of bloodstream and central nervous system infections caused by contrast solutions contaminated with *S. marcescens* after pain management procedures was also described in the USA (Cohen *et al.*, 2008).

### **Wound infections**

Surgical site infections (SSIs), associated with *Serratia* are common. The typical symptoms of wound infection include fever, pus, redness,

pain, and/or swelling. These infections are dominantly exogenous, and their origin is typically in the hospital environment. A healthcare-associated outbreak, caused by contaminated saline bottles used for wound cleansing in a wound care unit was registered in 2017 (Us *et al.*, 2017). Gery *et al.* (2021) reported an outbreak of postoperative infections due to the use of a contaminated T-shaped intraoperative probe. In 2020 there was a registered SSI outbreak in neurosurgery and orthopedics, caused by contaminated brushes impregnated with degerming chlorhexidine (Psaltikidis *et al.*, 2022).

### **CNS infections**

Rarely, *S. marcescens* has also been identified as a causative agent of meningitis and brain abscesses. Patients with head trauma or after neurosurgery, lumbar puncture, or epidural injections have been reported to be at higher risk for such infections (Wu *et al.*, 2012). Symptoms include fever, headache, stupor, vomiting, coma. A meningitis outbreak in patients after spinal anesthesia for caesarean section, due to contaminated medications for the procedure has been described. *S. marcescens* was isolated from prefilled syringes and a bag containing 5% dextrose with norepinephrine, suggesting that medications were contaminated extrinsically (Ersoz *et al.*, 2014).

### **Bone and joint infections**

Most commonly, *Serratia*-associated osteomyelitis and arthritis develop after hematogenous spread in intravenous drug abusers or may be presented as exogenous infections after surgery, blunt trauma, or intra-articular injection. Even though there are a limited number of sacroiliitis cases reported over the past 50 years. A recent case of *S. marcescens*-associated sacroiliitis was described in 2020 by Simon El *et al.* (2020) in the USA. Fever, lower back pain, referred hip pain, and weight-bearing difficulty were the major reported symptoms. The patient had a medical history of pilonidal cyst removal, *Klebsiella pneumoniae* bloodstream infection two years prior, Hepatitis A and C, and polypharmacy abuse. Having in mind the rarity of sacroiliitis infections, the difficulty in diagnosing, and even more isolating *S. marcescens* as a causative agent, this case is of great interest (Simon *et al.*, 2020).

### **Ocular infections**

The ocular infections, associated with *S. marcescens* are relatively rare. The endophthalmitis is usually associated with previous eye surgery even though there is a case of endogenous endophthal-



mitis after bacteremia (Poon *et al.*, 2013). Conjunctivitis and tear duct infections have also been observed (Liu *et al.*, 2005). In Bulgaria, Dubov and Marinova reported a case of bacterial hypopyon keratitis, associated with the use of contact lenses for 8 years. The patient was presented with irritation, watering, and redness in the left eye (Dabov *et al.*, 2016).

### Skin and soft tissue infections

The incidence of skin and soft tissue infections caused by *S. marcescens* is low. These infections are diagnosed mainly in immunocompromised or patients with pre-damaged skin and pre-existing ulcers and generally are associated with prolonged hospital stays (Us *et al.*, 2017). Soft tissue infections are demonstrated mostly as cellulitis and phlebitis (Soria *et al.*, 2008). In a recent case report, Francesca Genera *et al.* presented a young healthy, and immunocompetent adult with cutaneous infection, demonstrated with multifocal *S. marcescens* - associated painless, erythematous indurated plaques and papules (Genera *et al.*, 2022).

### Neonatal infections

Apart from the *S. marcescens* outbreaks in different clinical wards, there are many reported outbreaks in neonatology and pediatric departments all over the world, usually prolonged and difficult to control (Morillo *et al.*, 2018; Redondo-Bravo *et al.*, 2018; Muyldermans *et al.*, 2021). The main risk factors are the immature immune system, low birth weight (<1500 g) in preterm newborns, length of hospital stay, and use of antibiotics (Cristina *et al.*, 2019). In Italy for 10 years *S. marcescens* infection occurred in 127 neonates - 43 developed clinically significant infections and 3 of them died. The infections differed in severity and localization. The most severe fatal cases were sepsis and pneumonia (Casolari *et al.*, 2005). Arslan *et al.* described a sepsis outbreak that involved seven newborns, due to the administration of contaminated parenteral nutrition. Other factors were inadequate surface disinfection and poor staff hand hygiene (Arslan *et al.*, 2010). An outbreak involving a total of 59 neonates is also described in Spain. Twenty-five neonates sustained an infection, most frequently conjunctivitis and sepsis (Redondo-Bravo *et al.*, 2019). In a study by Madani *et al.* (2011) an outbreak involving 11 babies in a Neonatal ICU and three babies in a nursery, infected with *S. marcescens* at a University Hospital in Saudi Arabia was described. Newborns had septicemia, purulent conjunctivitis, urinary tract infection, meningitidis, and cellulitis.

One baby died from *S. marcescens* meningitis and septicemia. The source of infections was traced to contaminated baby shampoo introduced to the units five days before the first reported case (Madani *et al.*, 2011). In Bulgaria, an outbreak with 8 infected newborns was documented in 2007. The hands of the medical staff during medical manipulations (stomach aspiration procedures and first care for the newborns) were identified as the infectious source (MHB, 2007). In addition, the respiratory or gastrointestinal tract colonization by *S. marcescens* in the affected newborns was also found to be one of the main sources of infections.

### Conclusion

During the last decades *S. marcescens* has been proven as an important opportunistic pathogen causing a variety of hospital-acquired infections and outbreaks, mainly in immunocompromised patients, newborns, and patients after different medical interventions. Taking into consideration the severity and high mortality rates, associated with these infections and the trends in the last years of increasing resistance in clinical isolates of *S. marcescens* against strategic antimicrobials, strict infection control measures should be widely implemented to limit the hospital dissemination of this problematic bacterial species and to reduce the rate of *S. marcescens* associated infections.-

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